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THE

AMERICAN JOURNAL

OF THE MEDICAL SCIENCES

MAY, 1925

ORIGINAL ARTICLES.

CARCINOMA AND SARCOMA OF THE ESOPHAGUS: A PLEA FOR EARLY DIAGNOSIS.

By Chevalier Jackson, M.D., Sc.D.

(From the Bronchoscopic Clinic, Philadelphia.)

Malignant disease of the esophagus with its 100 per cent mortality is one of the greatest reproaches to surgery today. In almost all other fields at least a few cases are cured. While I cannot bring forward a method of cure, I can, I think, show why the surgeon has never had a fair chance to attempt the cure of these wretched sufferers inevitably and invariably doomed to a slow and painful death.

In every form of visceral cancer the surgeon never had a chance to obtain curative results of value until there were developed reliable means of affording a positive diagnosis before it could be made by the classic "history of the case, pain, hemorrhage, emaciation and cachexia." Surgical treatment of cancer of the esophagus is still floundering in this slough of despond, notwithstanding the fact that a means of diagnosis is available by which an endoesophageal cancer no larger than a pea can be diagnosticated with a certainty that is as close an approach to infallibility as anything known to medical science.

The reason for this sad state of affairs is that the textbooks and most of the journal articles still ignore or slight the only early means of diagnosis and advocate exclusively or chiefly the methods of diagnosis that are *always negative in the early stages of the disease.* How, under these circumstances, is a surgeon ever to have a chance to deal with the disease in the early stages?

The ultimate history of nearly every case of cancer of the esophagus shows it to have been classed as a medical case until the patient was moribund from food and water starvation, cachexia, metastases and suffering. Then the surgeon was called in to do a gastrostomy on a dying man. Naturally the surgeon is not very enthusiastic over the results obtainable by gastrostomy on such a patient; and it is hopeless for him to try to develop a curative operation which of necessity is a major one, on such clinical material.

The responsibility for this state of affairs rests not upon the practitioner, nor upon the internist, nor the surgeon, but rather upon the general failure to recognize the fact that, while esophagoscopy is a rapid, safe and almost infallible means of making a diagnosis, it is so only in the hands of those who have sacrificed the time necessary to master the few but essential details of its technic. In the hands of the untaught, esophagoscopy is a dangerous and misleading means of diagnosis. The fault then is that too few men have considered it necessary or worth while to learn how to do esophagoscopy, and especially how to avoid the serious and fatal complications that are sure to follow, in a certain percentage of cases, the uninstructed attempts to pass the esophagoscope.

Blame for previous lack of courage to urge the need for training before attempting esophagoscopy rests heavily upon the author.

Etiology, Incidence and Location. *Irritation and Preëxistent Disease.* This is not the place to discuss the unsettled question of the etiology of cancer in general. It is conceded that irritation can be a factor in the localization if not in the actual cause of cancer (Coplin,[29] Ewing[5] and others). The irritations peculiar to the esophagus are: (*a*) Those incidental to the passage, or, (*b*) stagnation of foods, and to the (*c*) regurgitation of the acid contents of the stomach. Our statistics show a preponderance of cancers at the lower end of the esophagus, which is the region most subject to irritation by all three of these factors. Statistics of cases in Scotland and in China, as pointed out by A. Logan Turner,[1] J. S. Fraser,[2] W. T. Gardiner[3] and G. Ewart Martin,[4] show a preponderance (2 to 1) of cancers in the upper third, and especially in the postcricoidal region, some indeed involving the hypopharynx. This preponderance is regarded by the authors referred to as possibly caused by the drinking of excessively hot tea by women of the working classes. This is especially striking because the total incidence of cancer of the esophagus shows relative rarity in women. The high cancers of the esophagus in China referred to by some authors as due to the eating of excessively hot rice is a very important observation, but is not quite so striking because of the preponderance in men; but there seems to us little doubt that the relative insensitiveness of the esophagus to hot food or drink exposes it to injury from this cause in persons who have learned the trick of get-

ting the hot food or drink past the relatively very sensitive anterior portion of the tongue.

One factor in irritation is stagnation. The esophagus normally empties itself downward without delay. If this is interfered with it tries to empty itself upward by regurgitation. Unlike the stomach, continued contact of food is abnormal and irritating. When to this are added the irritants quickly developed by fermentation of the stagnant food, we have an extreme degree of irritation that results in congestion and chronic esophagitis, as observed with the esophagoscope in hundreds of cases. While we have abundant esophagoscopic evidence of this static esophagitis and irritation as a factor in increasing the degree of stenosis and the rapidity of growth of cancer, our records do not indicate precancerous stenosis as a cause of cancer, certainly not as a frequent cause. Only about 5 per cent of our cases gave a history indicating any delay in swallowing prior to what might be considered the onset of the cancerous obstruction. The 5 per cent of cases in which a preceding stenosis was probable includes cases of lye burns, pulsion diverticulum, probable luetic stenosis, probable spasmodic stenosis and preventriculosis (so-called "cardiospasm"). In 2 cases histologically proven and ultimately fatal, cancer developed at the edge of a pulsion diverticulum. It thence descended into the esophagus in 1 case; the other was not esophagoscoped later, but may have extended in the same direction. In 3 other cases the history and enormous diffuse dilatation indicated a preventriculosis (so-called "cardiospasm") as a predecessor of adenocarcinoma at the hiatal level. In making deductions as to preëxisting stenotic disease, it is well to include only cases in which there remains objective evidence of the preëxisting lesion. Esophageal cancer, if free from the synergistic starvation, badly balanced diet and local irritation, is a disease of slow progress. We have had cases survive as long as five and six years.

Our statistics approximately agree with those of practically all other observers in the preponderance of cancer at the normal points of narrowing, the cervical portion, the crossing of the left bronchus and the hiatal level. The region of the crossing of the left bronchus is often referred to as the level of the aortic arch or the bifurcation of the trachea. The physiologic narrowing in this region, however, corresponds to the crossing of the left bronchus, as observed at esophagoscopy, which is the only reliable means of getting such anatomic data in the living. The left bronchus presses toward the spine; the aorta at a slightly higher level displaces sidewise toward the soft tissues. No fault can be found with the theory that these narrowings expose the mucosa to greater irritation than the intervening portions, and the clinical history of cancer almost everywhere in the body shows a predilection for sites particularly exposed to irritation (Coplin,[29] Ewing[5]).

In sarcoma, especially lymphosarcoma, long-continued irritation and chronic irritation are conceded causes; but our 3 cases of sarcoma of the esophagus afford no evidence as to etiology. The lesion in 1 case of lymphosarcoma was not primary in the esophagus.

Age is undoubtedly an etiologic factor. Our youngest patient with cancer of the esophagus was nineteen years old, another patient was twenty-six years old; all the others were over thirty. About 75 per cent of the patients were between forty and sixty years of age, the sixth decade of life being the most susceptible. Our youngest patient with sarcoma of the esophagus was a boy, aged six years; another patient was thirty-two years; one patient with lymphosarcoma was aged forty-three years, the other, sixteen years.

Sex should be considered perhaps rather a cause of location than a fundamental factor in etiology, because the total incidence of cancer in the two sexes is not far from equal. The difference of cancer incidence in the esophagus in the sexes is very striking. In our cases men preponderate in the proportion of almost 9 to 1 (87 + per cent). The statistics of A. Logan Turner[1] show a preponderance of women, approximately 2 to 1. This preponderance of women, as pointed out by A. Logan Turner and J. S. Fraser,[2] may be related to the fact that the cancers were chiefly among women of a class who drink frequently of tea excessively hot, a habit not prevalent among men in the same region. Viewed in this light the large incidence in women is not directly a matter of sex. The converse is true in China, where excessively hot rice is eaten by the men (Fraser[2]).

Anomaly. In 1 of our cases we found a fistulous tract lined with apparently normal epithelium, situated about 2 cm. proximally from the upper border of the growth, in the middle third of the esophagus. Whether there was any etiologic relationship or not, we of course cannot say. The fistula seemed blind at its lower end on insertion of a fine forceps closed; no lower orifice could be demonstrated.

In 2 of our cases of histologically proven cancer the sections showed mucous glands similar to those normally present in the gastric mucosa. These embryonal errors may have been factors in the etiology of the malignant lesion by an inherent low resistance. It is more likely, however, that, as stated by James Ewing,[5] "the sudden transition of epithelial types which they present offers a predisposing factor for epithelioma." In this connection it is interesting to note that of 16 cases of peptic ulcer of the esophagus at the Bronchoscopic Clinic, 6 were associated with the gastric glandular type of mucosa, as elsewhere reported.

Pathology. *Type of Growth.* In 671 cases in which a specimen was taken and reported upon as malignant the types of growth found were as follows:

Squamous-celled and atypical epithelioma	337
Basal-celled	2
Adenocarcinoma	316
Lymphosarcoma	2
Round-celled sarcoma	2
Fibrocarcinoma (epithelioma developing on scar?)	1
Squamous-celled, plus gumma	1
Squamous-celled, plus tuberculosis	1
Mixed, type uncertain	2
Ulceration but probably malignant	7

The foregoing does not include cases in which the specimen was reported negatively for malignancy, because in no such case did the progress, or any other phase of the case justify its inclusion in a list of malignant cases. The adenocarcinomatous type of growth was located in the lower third in almost all the cases. The squamous-celled type was found at all levels, but chiefly in the upper two-thirds.

Sarcoma of the esophagus has been observed 4 times at the Bronchoscopic Clinic. One of these cases has already been reported.[6]

Mixed Lesions. That tuberculous, luetic and cancerous processes can be combined in a mixed lesion in the esophagus, though rarely, has been established. That any 2 of the 3 may be combined has also been established and is less rare than the triple combination. For an excellent review of this subject, with a comprehensive bibliography and the complete report of a well-studied case, the reader is referred to the article by L. W. Dean.[7] Our statistics show a combined lesion of lues with cancer and of tuberculosis with cancer, but not of all 3 in one lesion in the esophagus.

In 14 of our cases of histologically proven cancer a strongly positive Wassermann reaction was obtained. All of these patients had dysphagia. Antiluetic treatment improved the ability to swallow in 10 of the patients, but as gastrostomy was done in 4 and in all the others the diet was regulated to prevent stagnation by eliminating milk and solids, the improvement cannot be taken as conclusive evidence of a luetic lesion of the esophagus. In 1 case, however, the diminution of a large mucosa-covered nodular mass on the left wall (10, Plate II), as seen esophagoscopically after two months of saturation with mercury (11, Plate II), corroborated the diagnosis of a combined luetic and cancerous lesion. This patient ultimately died of cancer.

In another of the cases with a strongly positive Wassermann reaction the histologic examination by Dr. Ernest W. Willetts showed, in addition to a typical squamous-celled cancerous process, in an adjacent portion of the specimen of tissue, free from epithelial infiltration, the vascular changes usually associated with lues and necrotic tissue suggestive of gumma. No spirochetes or bacilli could be demonstrated. Tuberculosis could not be excluded histologically, but no clinically demonstrable tuberculous process existed elsewhere in this patient. It seemed justifiable to consider

this case one of combined lues and cancer of the esophagus. He died ultimately of what was reported by his physician to be salvarsan poisoning.

In a third case of strongly positive Wassermann esophagoscopy showed a reappearing purulent discharge from a fistulous opening with a mass of granulations at the margin. Tissue removed from this granulating area, examined histologically by Dr. Ernest W. Willetts, showed typically tuberculous elements, though no bacilli were demonstrable in the tissue. One week later another esophagoscopy was done. A small tube (7 mm.) was used to pass the suppurating area. The lower margin of the lesion was found bleeding freely from a granular area, from which a second specimen was taken. The esophagus at this point was tightly strictured by a firm infiltration of the entire wall. The second specimen removed showed typical squamous-celled epithelioma. This patient had an advanced pulmonary tuberculosis with an abundant positive sputum. This was undoubtedly a combined tuberculous and cancerous lesion, though which was primary it is impossible to say.

In a fourth case, with strongly positive Wassermann, a squamous-celled epithelioma was found with a scar at its margin. Whether or not the scar was a cicatrized luetic lesion could not be determined. There was no history of swallowing a corrosive nor of difficulty in deglutition. The primary luetic lesion dated back twenty years. There was a small sacculated aortic aneurysm; the lungs were normal.

In 2 other cases in which a diagnosis of pulmonary tuberculosis had been made, with a dysphagia supposed to be adenopathic compression, esophagoscopic examination revealed an extension of malignant disease primary in the lung; in 1 case a glandular-celled carcinoma, in the other a lymphosarcoma. In both cases the pulmonary lesion was revealed by bronchoscopy. Without a diagnostic bronchoscopy neoplasms of the lung are often treated for months, even years, under a mistaken diagnosis of tuberculosis.

Multiple Primary Growths. In 2 of our cases two apparently separate lesions were found, the one about 2 or 3 cm. below the other, specimens from each showing the same type of growth, squamous-celled epithelioma. The esophageal mucosa between seemed normal. Whether or not they were instances of implantation metastases or of primary foci it is impossible to say; but there was no doubt about the isolation of the respective lesions so far as gross esophagoscopic appearances of the mucosa were concerned. The same condition may have existed in other cases, but it is only rarely that a cancerous growth is seen early enough to pass beyond it for exploration of the subjacent esophagus.

Metastases. Our records are so incomplete on the matter of metastases that it would be very misleading to give a summary. Unless the metastases were palpable in the neck, revealed in the ray or at the relatively few autopsies, no note was made.

Ulceration was present in most of the late cases of endoesophageal growths. It was more often apparent at peroral esophagoscopy than at retrograde esophagoscopy, It would seem, therefore, that the upper margin of the growth ulcerates earlier than the lower margin. In some cases the ulceration seemed to be an extensive melting away of the tissues with deep, sloughing, very foul areas. Some of these cases had a lumen larger than normal and had no dysphagia.

Location of the lesions in reference to the region is referred to under etiology. The location as to endoesophageal or periesophageal growths could not be determined positively in many of the cases because of the lateness of the stage of the disease at which the patient came in. The histologically evident types of structure, given in a foregoing paragraph, justify the inference that most of the esophageal growths start in the esophageal wall, and chiefly in the mucosa.

Symptomatology. *Early Symptoms.* It would be better for suffering humanity if all mention of symptoms were omitted with the exception of those listed below as "early symptoms." Practically all other symptoms are so late that to enumerate them serves only to perpetuate the fatal fault of late diagnosis on which the present 100 per cent mortality of this disease depends. These symptoms may seem trifling and vague—and they *are* trifling and vague—so much so that the patient often fails to notice them or is ashamed to mention them, and the practitioner either ignores them or attributes them to hysteria or morbid introspection. Often the patient is given a tonic at the only stage in which there will ever be any hope of curing the disease. These most important early symptoms are not mentioned in the textbooks or journal articles. They are described by the patient in such vague and varying terms that it is difficult to formulate them; but we shall give them as nearly as possible in the patient's own words. In most instances these symptoms had not been connected by the patient directly with the later trouble and were recalled only after close questioning:

1. "Slight, queer feeling in swallowing; but food went down all right."
2. "A feeling of nervousness about starting to swallow; after starting, food went down without any trouble."
3. "A feeling of nervousness in the neck."
4. "Vague sensation about the neck as of something wrong."
5. "A feeling of cramp around the neck."
6. "A feeling as if my swallow was not working right, but nothing seemed to stick until here lately."
7. Food "sticking in the throat while eating in a hurry; but it went down itself all right, and I had no trouble for months afterward; though I did not eat in a hurry any more."

8. "A feeling as of a lump rising in my throat." This occurred in many cases. In some patients it had no relation to eating; in other patients it occurred at sight of food or thoughts of eating; in other patients at the beginning of a meal, but disappearing after a few mouthfuls had been swallowed.

The foregoing early symptoms were elicited by close questioning of the patients as to the onset of the disease. The patients were not sent in during this initial stage because neither they nor their physicians realized the importance of the symptoms. Many patients have stated that their physicians had said the trouble was "just nervousness." Evidently it was considered a "globus hystericus." This condition we know, even when occurring as a manifestation of hysteria, to be not imaginary, but a spasmodic contraction of certain cervical or pharyngeal muscles, usually including the cricopharyngeus;[6] and such it seems to be in cases of foreign body and of organic disease of the esophagus, such as malignancy. When the spasm is excited by a malignant lesion this lesion is quite as often in the lower two-thirds of the esophagus as close to the cricopharyngeus muscle. In the cases in which the just mentioned vague statements were made by the patients the cancer was in most instances in the thoracic esophagus. This is not remarkable when we recall the insensitiveness of the thoracic esophagus and indefiniteness of localization of subjective sensations in this region. For instance, pain from a lesion in the thoracic esophagus may be referred to the back, the epigastrium, the neck, the shoulder, or even to some more remote location.

Cough is sometimes an early symptom. Most cases of unexplained cough should be esophagoscoped as well as bronchoscoped.

Late Symptoms. It would be better for the development of thoracic surgery, and for the ultimate good of humanity, if the late symptoms were not mentioned at all. It is necessary, however, to include them here in order to present the palliative methods that have been found to prolong life and lessen suffering in the cases that have come to the Bronchoscopic Clinic.

Dysphagia, odynphagia, pain, weight loss, hematemesis, emaciation and cachexia are all hopelessly late, so far as any attempt at cure of malignancy is concerned. When encountered, however, they call loudly for immediate ray study and esophagoscopy to discover and cure benign conditions, and to establish early the palliative measures that will prolong life in hopelessly incurable, advanced cancer of the esophagus. Dysphagia, when fully developed and prominently complained of by the patient, means obstruction; and obstruction in a loose bag like the thoracic esophagus means a well advanced lesion. Food will pass a small growth. Dysphagia is noticed somewhat earlier in cancers at the cricopharyngeal and hiatal levels, but it is always a late symptom. One of the erroneous statements often made is that the dysphagia in

cancer of the esophagus is progressive. In reality, as clearly shown by our records, it is, in its early stages, much more often intermittent; so much so that one of the commonest errors in inferential diagnosis is to exclude cancer because of sudden, recent onset. Many times we have removed a bolus of food in what was supposed to be a foreign body case and found a well developed cancerous narrowing of lumen. The bolus of food had stuck either because excessively large, too hastily gulped, or too ill masticated to go through the lumen, which was adequate for better masticated food. Afterward static esophagitis and engorgement from irritation of the growth may perpetuate this suddenly appearing dysphagia. Often the artificial dentures or lack of teeth, incidental to the cancer age and conducive to ill-mastication, are blamed wholly for the stoppage; when in reality they are only partly responsible, and might even be regarded as a blessing in disguise, as giving to the alert practitioner an early sign of cancer of the esophagus. Only too often this early sign is ignored, sometimes even fatality results from an ill advised blind attempt to push the bolus downward with a bougie. Very frequently in cancer cases we get a history of such stoppage of a bolus which, however, had gone through spontaneously, resulting in an erroneous diagnosis of spasmodic stenosis by practitioners who did not realize that the day of inferential diagnosis of esophageal disease is past.

It is well to remember that dysphagia, odynphagia and spontaneous pain may be absent. In 22 of our cases the esophageal cancer had not produced any difficulty in swallowing. The lesion was discovered in the cervical esophagus in 16 cases referred for study as to the cause of a cervical adenopathy. In these cases the growth was small, but the metastatic leakage had been much earlier than is usual in the lower two-thirds of the esophagus. In the other 6 cases the absence of dysphagia was evidently due to the sloughing, liquefying nature of the growth. In these cases esophagoscopy was done in a search for the cause of melena.

Odynphagia and spontaneous pain are also very late symptoms, pain being later, perhaps, than in cancer in any other region of the body. There is, often, distress from irritation of stagnant food and coexistent esophagitis; but the typical cancer pain associated with cancer elsewhere usually comes very late. In many cases the pain is never so severe as that seen in peptic ulcer of the esophagus. Often the pain of cancer is less than that of esophagitis.

Hoarseness is nearly always present, in some degree, late in the progress of the case. Sometimes it is due to recurrent paralysis, as mentioned in the textbooks; but much more frequently it is due to an overlooked factor, namely, the overflow into the larynx of secretions and even of food and drink, owing to the subjacent esophageal obstruction. This most common cause of hoarseness has been overlooked in the literature. Occasionally it is due to

arytenoid fixation from direct extension into the laryngeal motor mechanism from postcricoidal cancer. When paralysis is present it is much more frequently unilateral than bilateral. Obviously paralysis can result only from growths or metastases high enough to involve the recurrent nerve fibers, roughly speaking, in the upper half of the esophagus.

Cough may be a late symptom from overflow of secretions into the larynx, because of absent or defective esophageal drainage of normal secretions. This mechanism is often overlooked. In some cases a severe laryngotracheobronchitis may result. Cough may also be present as a reflex from the neighborhood of the growth. Cough, productive of secretions, blood or food, may be present from erosion of the growth through the wall of the trachea or a bronchus, oftener the left, or, occasionally, into the parenchyma of the lung, oftener the right.

Diagnosis. There are only two means by which an early diagnosis of cancer of the esophagus can be made, namely:

1. Roentgen-ray examination.
2. Esophagoscopy.

Only by these means will the diagnosis ever be made early enough to give the surgeon a chance to develop the technic of a curative operation; only by these means can efficient palliation be started in time to prolong the patient's life. All other means are *always negative in the early stages.*

Roentgen-ray Examination. All esophagoscopists will agree with Ellen J. Patterson[8] that roentgen-ray examination should always precede the esophagoscopy. In most cases the roentgenologist's diagnosis will be correct; for absolute certainty esophagoscopy should follow the roentgen-ray examination. The fluoroscopic examination will reveal the esophagus in action; in other words, it permits examination of the *function* of the esophagus—something that cannot be got in any other way, not even with the esophagoscope. The fluoroscopic examination will not only often reveal evidence of malignancy, but it will exclude aneurysm. This condition is not a contraindication to esophagoscopy, because no esophagoscopist would poke his tube into an aneurysm involving the esophagus, which, of course, he can plainly see ahead of his tube-mouth; but when the fluoroscopist reports a sacculated aneurysm against which the opaque mixture stops, or past which it slowly trickles, the diagnosis has been made and the indications for treatment are plain.

Ray films, especially a well made stereoscopic pair, interpreted by an experienced roentgenologist, afford a very reliable means of diagnosis, and, taken with the fluoroscopic findings, the ray diagnosis will rarely call for revision. One invaluable diagnostic point afforded by the ray is information as to the lateral extent of the growth.

This information can be had in no other way. As to the technical consideration of roentgen-ray diagnosis the reader is referred to to the articles by Manges,[9] Pancoast,[10] Pfahler,[11] Bowen,[12] Hirsch[13] and many other scientific and skilful roentgenologists who have studied this problem and developed the technic to its present point of practical perfection.

It is necessary here to emphasize the necessity of attaching no importance whatever to negative ray findings except those of experts with the best apparatus. Many hospitals are handicapped in being unable to afford the best and latest of the frequently improved apparatus. Under these circumstances it is especially necessary to beware of negative findings. Even under these circumstances, if they cannot be bettered, it is in all cases necessary to resort to the ray examination as the first step in the diagnosis.

Esophagoscopy. This is the final arbiter which gives all the certainty of direct examination with the eye, yielding objective evidence that, taken with the roentgen-ray examination, which is also an objective method, relegates all inferential methods to third place, if not to desuetude. All inferential methods, including the bougie, depend upon obstruction, whereas with the esophagoscope the walls of the esophagus are examined for the presence of lesions. Every crease and fold is exposed to inspection by the eye. The great safeguard in esophagoscopy as compared with the bougie and all similar methods is that you can see what is ahead of the distal end. You do not push when you see tissue, normal or abnormal, ahead of the tube-mouth. By the esophagoscopic appearances alone the diagnosis has been correct in about 92 per cent of the cases of endoesophageal cancer at the Bronchoscopic Clinic, inconclusive in 6 per cent, unconfirmed in 2 per cent. These figures omit consideration of biopsy; in no instance has a positive histologic diagnosis of cancer been proven erroneous.

With the esophagoscope we have been able to make a diagnosis before the stenotic stage in 28 patients, and we have every reason to believe we could have made it thus early in practically all the cases of esophageal disease that started endoesophageally if they had reached the esophagoscopist early.

If for any reason a first esophagoscopy is inconclusive, a second esophagoscopy or as many more as desired may be done. Being done without anesthesia, general or local, and, if the patient is in good condition, without hospitalization, it has sometimes been deemed advisable to study a case at esophagoscopies repeated every week or oftener. Prolonged fasting is unnecessary; four hours are deemed sufficient after liquid food. In a few weeks esophagoscopic and roentgenologic study has usually sufficed to clear away all doubt even in the most obscure cases of periesophageal malignancy.

DESCRIPTION OF PLATE I.

ILLUSTRATION OF THE MISLEADING AND FATAL RESULTS OF BLIND BOUGINAGE FOR DIAGNOSIS. PAINTED FROM A POSTMORTEM SPECIMEN BY THE AUTHOR.

The patient had been admitted moribund with mediastinal hemorrhage and emphysema. The trachea is opened through the "rings" to the right of the membranous posterior wall; the larynx is laid open from behind; the esophagus is split down the right wall as far as the diaphragm. The perforation evidently had been made by a bougie, shortly before admission, causing the fatal mediastinal hemorrhage shown by the huge blood-clot. The edges of the perforation showed no histologic evidence of malignancy. The bougie had evidently gone through normal esophageal wall, where the lumen was not pathologically stenosed, above the cricopharyngeus, and far above the cancer, which is seen in the esophagus at the level of the diaphragm surrounded by a mass of lymph nodes under the pleura. The danger of perforation by a blindly passed bougie through cancerous tissue is frequently mentioned, but the greater danger of perforation of the perfectly normal wall is not so generally realized. It is also noteworthy that this patient was treated for a supposed "cardiospasm" at three different clinics before reaching the place where an erroneous diagnosis of cancer of the cervical esophagus was made because the bougie was arrested in the neck and came back bloody! No esophagoscopy was done in this case because the patient was dying when admitted.

PLATE II.

ENDOSCOPIC VIEWS OF CARCINOMA AND SARCOMA OF THE ESOPHAGUS.

These views were sketched by the author from memory shortly after the respective esophagoscopies, hence represent a view of the interior of the esophagus at a certain level in the particular cases, the patient being in the dorsal position in each instance. No anesthetic, general or local, was used, a fact which must be borne in mind when considering color. The sketches serve to illustrate the modern method of diagnosis of esophageal disease by looking at the lesion. They also show how accurately a specimen, when desirable, can be taken from any selected part of the lesion.

1. Normal esophageal folds as seen at the moment the esophagoscope enters the thoracic esophagus. The delicate pink, velvety surfaces, the soft folds flattening without resistance at the approach of the tube-mouth and yielding to the slightest manipulation of the tubal lip; the resilient respiratory recession and advance; the pulsatory movement of one wall at certain levels;—all these are, esophagoscopically, so characteristic of the normal esophagus, to the accustomed observer, that any abnormality in color, form or movement is instantly apparent. The sketch shows the image during the momentary pause at the end of the expiratory phase.

2. Whitish, nodular form of carcinoma on the posterior wall of the upper end of the esophagus in a woman, aged fifty-eight years, who for over a year and a half was thought to have had "spasm of the esophageal muscles." "cardiospasm," "neurasthenia," "major hysteria," finally "mental derangement," because of increasing "globus hystericus" and, later, "refusal" (!!) to swallow food, for which she was ultimately placed in a psychopathic institution. She was fed with a stomach-tube, the passage of which was thought to rule out organic esophageal disease. After having consulted specialists in various parts of the world she came under the observation of an internist who at once decided the esophagus should be looked at with the esophagoscope. It required thirty seconds to find the lesion, make an esophagoscopic diagnosis of cancer and take a specimen, which Dr. B. L. Crawford found to be a squamous-celled epithelioma. The symptomatic simulation of a neurosis by cancer of the esophagus is very frequently observed by esophagoscopists.

3. Cancer of the thoracic esophagus in a man, aged twenty-six years, sent in with a diagnosis of "cardiospasm." Form more often than color is the esophagoscopic criterion of malignancy. The anterior (upper) fold is not very different in color from the normal mucosa, but it is granular, almost nodular, with fungations which at a later stage are often quite exuberant. The creases between the folds are filled with oozing blood.

4. Cancerous infiltration of the thoracic esophageal wall in a man, aged forty-five years, supposed to have spasmodic stenosis in the middle-third of the esophagus. Here again the color of the mucosa was not far from normal; but the hardness, the rigidity, the absence of the normal characteristics of movement incidental to respiration, pulsation and manipulation described above (1) were deemed so characteristic of malignant infiltration that an esophagoscopic diagnosis of cancer was made. As it was deemed inadvisable to take a specimen at this stage, it was

PLATE I

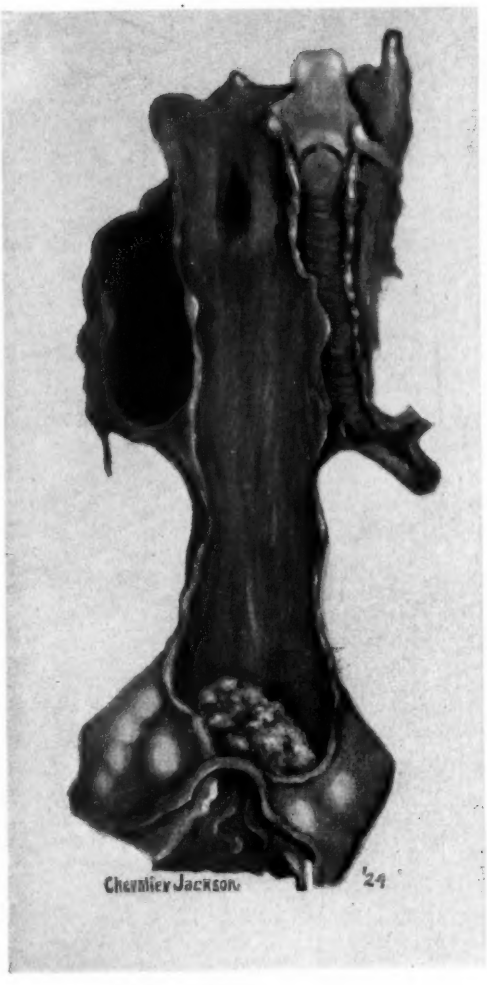
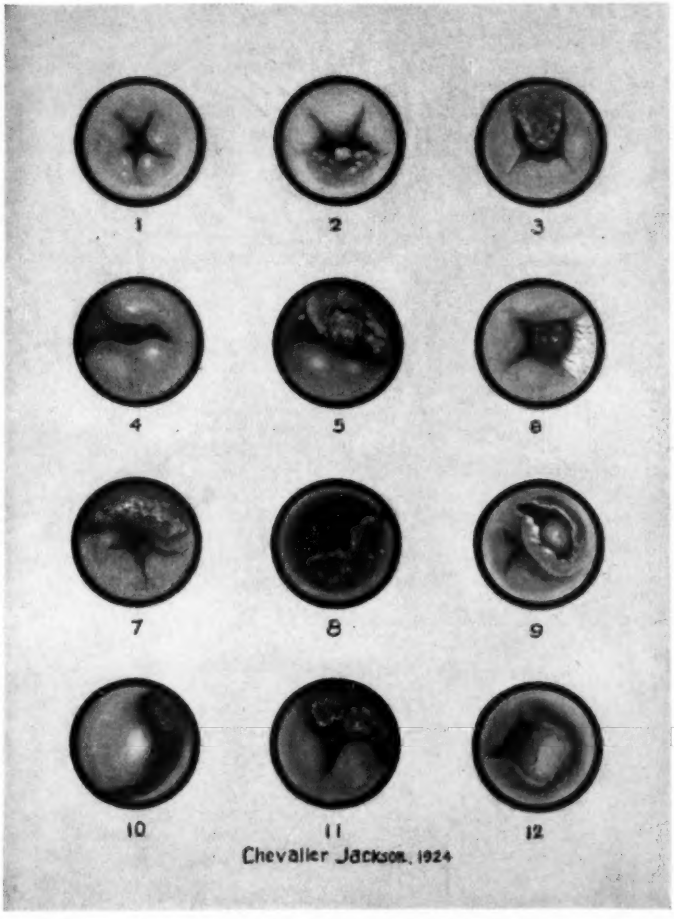


PLATE II



requested that the patient be sent back in six weeks. (See the legend to the following illustration, 5.) An esophagoscopic diagnosis of malignancy was made, however, on the conditions here described, and an immediate gastrostomy was advised, but was postponed.

5. Same patient as in the preceding illustration (4). The anterior rounded ridge of infiltration has ulcerated; a center slough, discolored with bismuth sulphide, is ready to come away. The edges are beginning to fungate, which renders the taking of a specimen perfectly safe. This was done, and Dr. B. L. Crawford reported upon the specimen, squamous-celled epithelioma. The relatively rapid progress of the ulceration was probably due to the constant presence of stagnant, fermenting, irritating food.

6. On the right wall is seen an old scar. This was probably due to the swallowing of lye, twenty years before, of which there was a very clear history. The bleeding fungations at the distal edge of the scar looked so suspicious of malignancy that they were nipped off and sent to the laboratory. Dr. Ernest W. Willetts reported upon the specimen as undoubtedly squamous-celled epithelioma.

7. Boy, aged sixteen years. Lymphosarcoma involving the anterior wall of the esophagus, at the level of the crossing of the left bronchus. This patient had no difficulty in swallowing. He was supposed to have asthma, causing him to "wheeze and to cough until he vomited." He was referred for bronchoscopy because of the asthmatic symptoms. The bronchoscopic findings shown in the following illustration (8) led to the esophagoscopy. Air-bubbles were seen at the depressed necrotic area, and a hissing sound was heard through the esophagoscope when the patient voluntarily coughed at request. Part at least of the dark grayish color of the exudate is due to sulphided bismuth.

8. View down the left main bronchus of the patient referred to in the preceding illustration (7). The bleeding granular mass on the posterior wall of the bronchus evidently was part of the growth visible esophagoscopically (7). What appears like a grayish slough was partially sulphided, swallowed bismuth that came through from the esophagus. Blood was oozing among the fungations.

9. Woman, aged forty-two years. Difficulty in swallowing diagnosticated cancerous on three previous occasions because of arrest of the bougie, the tip of which came back bloody, and of the history of progressive dysphagia and emaciation. The yellow, globular mass protruding in the ragged, irregular opening was scooped out with the mechanical spoon and found to be cheesy débris and thick pus, with a few giant cells and elements of glandular structure. No tubercle bacilli were found, but Dr. Ernest W. Willetts deemed the process suppurating tuberculosis of the mediastinal glands rupturing into the esophagus. There was no clinical or ray evidence of active pulmonary tuberculosis. Dr. Russell H. Boggs stated that there were slight indications of healed apical lesions. The patient made a good recovery, with normal swallowing, and was above normal weight four years later.

10. Man, aged forty-seven years. Gastrostomy had been done before admission. This illustration shows a mixed lesion, luetic and cancerous. The large, smooth, rounded mass on the left wall was not very hard and was movable with the tube-mouth. Because of the 4 + Wassermann reaction it was deemed best not to take a specimen. The patient was put upon energetic antiluetic treatment, which resulted in the total disappearance of the dysphagia.

11. The same patient as in the preceding illustration (10); esophagoscopic appearances after two months of energetic antiluetic treatment (KI and Hg prot.). The nodular mass, which was probably a gumma, is seen to have disappeared; but the granular mass has increased in extent and is fungating exuberantly and oozing blood freely. Three endoscopists at the Bronchoscopic Clinic were unanimously of the opinion that the fungating lesion was cancerous. This diagnosis was doubted by the attending physician because of the total disappearance of dysphagia under antiluetic treatment, the gastrostomy tube having been entirely abandoned. A specimen was therefore taken and was reported by Dr. Baxter L. Crawford as squamous-celled epithelioma. The progress of this case confirmed this diagnosis.

12. Peptic ulcer of the esophagus in a man, aged forty-seven years, suffering from dysphagia, odynphagia, severe nocturnal substernal pain extending through to the back. These symptoms, with obstruction to the passage of a bougie which came back bloody had led to the diagnosis of cancer of the esophagus. The patient was emaciated apparently from pain, sleepless nights and worry in anticipation of a death by cancer, rather than from lack of nourishment. The border of the ulcer was not hard and a small esophagoscope would pass it, going on through the hiatal esophagus into the stomach, which was about eight centimeters below the lower border of the lesion. A specimen removed from the edge of the ulcer showed no evidence of malignancy; only inflammation and ulceration. Histologic elements of gastric mucosa and glandular structure led to the diagnosis of peptic ulcer of the esophagus, starting in an esophageal island of gastric mucosa.

To get a chance to make an early diagnosis of cancer of the esophagus, it is necessary to see patients before the development of more than a very slight degree of stenosis. As noted under symptomatology, very vague descriptions by the patient of early symptoms are often either overlooked or classed as "globus hystericus." It is to be expected that if every patient complaining of the vague symptoms referred to under symptomatology is esophagoscoped, many purely neurotic patients will be examined. But this is inescapable if cancer of the esophagus is to be diagnosticated early. Over and over again we have made an inferential diagnosis of globus hystericus, or of a neurotic condition, passed an esophagoscope and found a cancer of the esophagus. There is no way in which to distinguish between the globus of hysteria and the globus of organic disease except by the esophagoscope. As elsewhere herein mentioned, the opinion of the roentgenologist is often decisive as to purely neurotic conditions, and should always be had before esophagoscopy; but usually the roentgenologist will advise esophagoscopy also. In no case is full justice done to the patient in making an inferential diagnosis of globus hystericus without the ocular evidence afforded by the roentgen-ray and the esophagoscope.

Esophagoscopic Appearances. Endoesophageal malignancy develops at a very early stage characteristic and unmistakable appearances. These have been fully described (Jackson[6]), and are well known to esophagoscopists. Anyone who has seen many cases of cancer in the pharynx and who is also accustomed to monocular vision through an endoscopic tube, will rarely, if ever, fail to recognize ulcerative, fungating cancer of the esophagus, such as illustrated in Plate II. Some delay in esophagoscopic diagnosis arises in the periesophageal growths producing a compression stenosis of the esophageal lumen. In these cases the presence of a hard stenosing mass palpable with the tube-mouth outside the wall and obliterating the soft, resilient unfolding of the normal esophageal wall (1, Plate II) is diagnostic to the experienced esophagoscopist. When these appearances are present the esophagoscopist will always consult with the roentgenologist who is able in practically every such case to outline the exterior border of a periesophageal growth. The internist will exclude pulmonary tuberculous and suppurative disease that might produce a secondary compressive adenitis, and lues will be excluded by the usual means.

Approached thus from four angles the diagnosis of periesophageal malignancy comes as near certainty as is possible in any neoplastic disease without biopsy. Certainly, the percentage of error will be small even if we were compelled to stop there. But in a large percentage of cases of periesophageal disease a subsequent esophagoscopy after a month or two will show the fungating form of lesion from which a specimen may safely be taken. Anyway, it is not in the periesophageal, but in the much more frequent endo-

esophageal cancers that hope of surgical cure lies. In considering esophagoscopic appearances it must be remembered that mediastinal abscess may compress the esophagus; but it is softer to palpation with the tube-mouth or swab. At a later stage, when the abscess has discharged into the esophagus, the orifice of the fistula may be confusing, especially if granulations are exuberant; but the oozing of pus is usually quite noticeable; and, most important, in all such cases it is at once manifest to the esophagoscopist that a specimen may be taken with perfect safety. The histologic report will be decisive. If the first specimen be inconclusive, a second, or as many as desired, may be taken at subsequent esophagoscopies.

Peptic Ulcer. There is only one condition with which cancer is likely to be confused in esophagoscopic appearances, namely, that rare condition, peptic ulcer. Minor mucosal erosions of the esophagus are relatively common, and aphthous ulcers are not very rare; but large, deep ulcerations are so rare that many esophagoscopists of large experience have not seen a case. In all there have been 16 of these cases that have come to the Bronchoscopic Clinic. All but 2 of them were in the lower third of the esophagus, and in 6 of them histologic structure suggestive of gastric mucosa was demonstrable. That all of them were located on islands of gastric mucosa is possible, but there was nothing to substantiate such a belief in any except the 6 cases. The esophagoscopic appearance of these peptic ulcers as elsewhere described by the author is not unlike the gastroscopic appearances of gastric ulcer. In all cases of suspected peptic ulcer of the esophagus, biopsy will decide with certainty.

Biopsy. In over 92 per cent of the cases the diagnosis by esophagoscopic appearances alone ultimately has been found correct. So far as a palliative treatment such as gastrostomy is concerned, no specimen need be taken, because such measures are strongly indicated anyway; but when it comes to a radical surgical procedure, such as transthoracic esophagotomy, the surgeon desires to have peptic ulcer, gumma, foreign body, esophagitis, cicatricial and spasmodic stenosis and other benign conditions excluded before undertaking a possibly fatal exploration. Histologic examination of an esophagoscopically removed specimen affords the absolute certainty that is necessary to get a man in good general health to submit to an operation of very high mortality. If the patient is not in good condition he will not survive the operation. During our more than thirty years' experience we have never had a histologic diagnosis of cancer based upon an esophagoscopically removed specimen found absolutely erroneous. Specimens sometimes are inconclusive, but when this occurs other specimens are taken. There are often cases in which we deem it unnecessary to take a specimen, and there are other cases in which we deem it unwise to take one. In the latter case a later esophagoscopy will usually reveal a lesion

from which a specimen may be taken with safety. No anesthetic, general or local, is used. Esophageal lesions, neoplastic or otherwise, are insensitive to the taking of a specimen of tissue.

Examination of the Patient. As just stated, esophagoscopy is the one great and only method without which a diagnosis of esophageal cancer cannot be made early and without which a diagnosis cannot be made with certainty, even late. If follows, therefore, that esophagoscopy should be done in every patient presenting any symptom whatever of the slightest abnormality in the swallowing function.

However, this does not mean that esophagoscopy is the first step in the making of a diagnosis. On the contrary, while it is first in importance, it is the last step in the orderly procedure by which a diagnosis of esophageal disease should be made.

The following are the steps in the procedure for the diagnosis of esophageal disease at the Bronchoscopic Clinic:

1. A complete history is taken.

2. Complete examination of nose and throat, including mirror examination as to: (*a*) Defective motility of the larynx, (*b*) infiltration from extension of a hypopharyngeal growth, and (*c*) accumulations of secretions in the pyriform fossæ, indicating impaired esophageal drainage. Any or all of these may indicate esophageal disease. Severe dysphagia and odynphagia may be due to disease, benign or malignant, of the epiglottis, pharynx or larynx.

3. Physical examination, complete, including careful examination of the lungs, heart, circulation, etc.

4. Urinalysis, sputum test, hemoglobin test, blood count, etc.

5. Wassermann test.

6. Fluoroscopic examination first for aneurysm, then with an opaque mixture, as to the functioning of the esophagus.

7. Roentgen-ray examination of the chest for disease of the pleura, lungs, heart and mediastinum as well as the esophagus; first without then with a swallowed opaque mixture.

8. Complete gastrointestinal ray study. This sometimes is omitted, but omission is seldom advisable unless a hopelessly advanced cancer of the esophagus is discovered by the previous ray study.

Positive findings in any of the foregoing examinations do not necessarily obviate the necessity for an esophagoscopy, nor contraindicate it. But extensive, painful, ulcerative tuberculosis of the epiglottis or larynx, for instance, with a fluoroscopically normal esophageal lumen and swallowing function, constitute a combination of evidence upon which we often decide not to do an esophagoscopy or to postpone it pending further observation. If, however, fluoroscopy shows narrowing of the mediastinal esophageal lumen, as by glands or neoplasm, esophagoscopy may be called for in cases with tuberculous laryngeal disease. In malignant disease of the larynx, unlike tuberculous laryngeal disease, esophagoscopy

is of the utmost importance to determine contraindicating metastases along the hypopharyngeal or esophageal wall. If there are nodular elevations or compression or infiltration of the wall of the thoracic esophagus indicating mediastinal metastases, laryngectomy is hopeless and contraindicated (Jackson[6]).

A patient with lues or pulmonary tuberculosis may have cancer of the esophagus. We have seen quite a number of such coincident diseases, though rarely as mixed lesions, as elsewhere herein mentioned. We often decide, in case of a strongly plus Wassermann test, to wait for a thorough course of mercury before doing esophagoscopy for diagnosis.

Errors in Diagnosis. Practically all the errors in diagnosis of esophageal malignancy arise from dependence on methods that are always negative in the early stages and on inference instead of objective evidence. Of 110 cases of esophagoscopically proven malignant disease of the esophagus, in 87 an inferential diagnosis of neurotic conditions had previously been made either by ourselves, tentatively, or by our predecessors tentatively or positively.

One of the most common errors in the inferential diagnosis of esophageal disease based on the history of the case is to exclude cancer in favor of spasm because of the patient's positive assertion that he never had any trouble in swallowing until a few days or weeks previously, when suddenly a piece of meat or other food stuck because insufficiently masticated. This sudden onset of symptoms is very common in cancer (Turner[1]). In many such cases at the Bronchoscopic Clinic we have found well-developed cancer which must have been present for many months. Any well-masticated food will, without difficulty, go through an esophageal lumen of 6 mm. diameter; yet an imperfectly masticated bolus will stick, for a time, at least. It is not until this happens that the patient's attention is called to any difficulty in swallowing. This explains the sudden onset. In other instances a sloughing type of growth may be at times only slightly obstructive. But why do the patient injustice of trying to make an inferential diagnosis of esophageal disease when the esophagus is open to direct examination of the eye by a simple and safe technic that requires no anesthetic, general or local, and no hospitalization; that involves no more annoyance than having a tooth filled; and that requires but a few minutes?

Apart from the vague "neurotic" symptoms elsewhere herein referred to, there is only one point in the history of the case that is of great importance in the early diagnosis of cancer of the esophagus, and that is the history of food having at some time or other stuck for a moment or longer. But this is not diagnostic. In other words the history of the case is of value chiefly as eliciting an indication for esophagoscopy. It cannot be too strongly urged that it should be part of all routine history taking in all hospitals

to ask every patient, regardless of the chief complaint, these two questions:

"1. Have you ever noticed any trouble in swallowing food or liquids?"

"2. Do you remember ever having had food lodge for a time before going down?"

All internes should be thus instructed and all printed instructions for the filling in of history blanks should have these questions printed on them. By this means opportunities for early esophagoscopic diagnosis would be afforded and many diagnostic errors would be eliminated.

In 12 cases of cancer of the esophagus coming to the clinic the patients had an enlarged and diseased lingual tonsil, and in 4 of the cases we felt inclined inferentially to regard this as the cause of the dysphagia of which the patients complained. In all 12 cases, however, esophagoscopy revealed a cancer in the esophagus. In a number of other cases, however, esophagoscopy showed the esophagus to be normal. Therefore while the lingual tonsil should always be thought of as a cause of dysphagia, as so well demonstrated by J. Arnold Jones,[14] every such case should be esophagoscoped. Endocrine disturbance, as suggested by Mr. Jones, may be very intimately connected with globus hystericus and the vague sensations often noted in such cases; but malignant disease of the esophagus occasionally at its very incipiency gives rise to sensations quite as vaguely described by the patient. If we are ever going to diagnosticate esophageal and hypopharyngeal malignancy early, almost all of these patients must be esophagoscoped.

One of the most frequent of diagnostic errors arises from the use of the blind bougie, which is in reality an inferential method. Those who use it infer that when it goes through there is no cancer, though it may have gone through the esophageal wall into the mediastinum, or have passed a small early or late sloughing nonobstructive cancer; if it meet an obstruction they infer that the obstruction is cancerous, even though the obstruction may be normal wall; if it show blood on withdrawal, they infer that the blood comes from a cancer and not from normal or inflamed mucosa; if it be foul they infer that the odor comes from an ulcerating cancer and not from stagnant food and secretions, or a septic mouth, or septic faucial lymphoid tissue. There have come to the Bronchoscopic Clinic 21 cases of cancer of the *lower* end of the esophagus in which an erroneous diagnosis of cancer of the *upper* end of the esophagus had been previously made by the bougie. These erroneous diagnoses were all made with localization at about 15 to 17 cm. from the upper teeth, which is the level of the cricopharyngeal fold. This region was found normal at esophagoscopy except in the cases in which a false passage was found.

All esophagoscopists agree with the following admirable sum-

mary of Mr. Tilley,[15] giving reasons why a bougie should never be used in a case of suspected cancer:

"1. It may fail to detect any obstruction when the growth is small, or even in advanced cases when rapid ulceration fails to produce stenosis.

"2. If an obstruction is met with, the bougie affords no more than presumptive evidence of its nature.

"3. Fatal results have followed the use of the bougie even in skilled hands, as a result of perforation of the thin diseased walls of the esophagus in the immediate neighborhood of the growth."

To this I should like to add a supplementary paragraph:

4. Fatal results have followed the use of the bougie as a result of perforation of the perfectly normal wall of the esophagus far above the growth in some cases, and in other cases in which no growth whatever existed.

Plate I illustrates a case of death from mediastinal hemorrhage due to blind bouginage in skillful hands. Arrowsmith[16] and many others have reported similar cases in the literature. Similar cases are shown by specimens in many large medical and surgical museums in this country and Europe. Trousseau said, in effect, that all these patients died sooner or later of the bougie.

If for any reason an esophagoscopist were unavailable we would abide by the decision of a competent roentgenologist, and under no circumstances would we submit our patient to the risk of the dangerous, inconclusive bougie.

Prognosis. It was stated by the author,[6] many years ago, that the mortality of malignant disease of the esophagus was, at that time, 100 per cent. Notwithstanding the great advances since made in the surgery of malignancy elsewhere in the body the ultimate prognosis of esophageal cancer remains the same today. There is every reason to believe, however, that the reason for this is that the surgeons have never had a chance to develop the technic of a curative operation because the diagnosis is never made early. The reason why the diagnosis is never made early is that the text-books and journal articles give chiefly or exclusively diagnostic methods that *are always negative early* in the disease. When the time comes in which esophagoscopy shall be resorted to promptly on the appearance of certain very vague symptoms there is ample justification for the belief that the surgeon will cure a good percentage of patients. Squamous-celled endoesophageal carcinoma is not an aggressive type of malignancy. On the contrary it is a mild, slow and for a long time purely local process. Under palliative treatment, if the patient is never permitted to be short of an abundance of water and a full allowance of properly balanced food elements, most cases will survive at least two years from the onset of the disease, and some have survived as long as five years. One lived six years. Patients running the gauntlet of late inferen-

tial diagnosis, and leading a precarious existence of various degrees of food and water starvation, depressed and acidotic, on a diet of intermittent supplies of raw eggs and meat broths, may not survive a year from the probable time of the onset of the disease.

Treatment. *Resection of the Esophagus.* Until some now unknown method of treatment of cancer of the esophagus shall have been discovered we must look to the surgeon for hope of cure. Nor should the gravity of the procedure deter us, since we know that the disease involves 100 per cent mortality. There is good reason to believe endoesophageal cancer is curable surgically, at some levels at least, if a sufficiently early diagnosis be made. The fundamental reason for the thousands of agonizing deaths from cancer of the esophagus is false education. The mind of the medical student and the medical profession is so saturated with the idea that cancer of the esophagus is to be detected by obstruction to the passage of a bougie, in a patient with dysphagia, pain, cachexia and emaciation, that the surgeon never gets a chance to cure esophageal cancer while it is still a local process. When every patient mentioning the slightest abnormality in swallowing, or even slightest abnormal sensation in the cervical, retrosternal or epigastric region, is considered not necessarily neurotic, but possibly cancerous, surgery will show better results. When such a patient shall be referred at once to the roentgenologist for fluoroscopic and roentgenographic study of the esophagus, esophageal cancer will be discovered early and a new era in esophageal surgery will have been established. In most of such cases esophagoscopy should follow the roentgen-ray examination, and always in all cases in which the roentgenologist suspects esophageal abnormality. Few surgeons today would wish to expose transthoracically the mediastinal esophagus with a view to resection for cancer without having the esophagoscopist's confirmation of the diagnosis. When a diagnosis can be made by other means it is not only uncertain, but the patient almost invariably has become a bad subject for a major operation. Practically all esophageal resections up to the present time are done upon such cases. It is no wonder the results are so discouraging. They would be so with cancer anywhere in the body.

The foregoing statement of opinion as to the surgical curability of early esophageal cancer is based not on cures, but on some of the findings at the Bonchoscopic Clinic, which may be summarized as follows:

1. Over 90 per cent of all the cases fall into two classes, namely:
   (*a*) Adenocarcinomata at the lower end of the esophagus.
   (*b*) Squamous-celled cancer in other locations.

2. This leads to the conclusion that the disease at the lower end of the esophagus started at the cardial margin. If discovered at the start, such cases would offer good chances of cure by exsection through an abdominal incision. We do not refer here to extensive gastric cancer reaching the esophagus very late.

3. The squamous-celled type, which with us has been the most common, means in most cases an endoesophageal beginning. Here we have a local process of a relatively low degree of malignancy. It is reasonable to expect a good percentage of cures if the surgeon could get the patient in this stage, but he never does, and never will, so long as present obsolete diagnostic methods are taught in the medical schools and promulgated in our journals and text-books. Our experience abundantly confirms the statement of Willy Meyer[17] when he says:

"There is one important characteristic of cancer of the esophagus that should be especially emphasized, namely, that it is the most benign of all carcinomas of the gastrointestinal tract. Its growth is comparatively slow; it remains localized for a long time; has little tendency to metastasis in other parts of the body, or in the lymphatic glands, and is not very apt to recur."

Splendid fundamental work in resection of the esophagus has been done by Torek,[18] Miller,[19] Meyer,[17] Janeway and Green,[20] Lilienthal,[21] Muller,[22] Hedblom[23] and others. The lacking essential is early diagnosis, which could be furnished by esophagoscopy not only early, but with the absolute certainty essential to getting the consent of a comparatively well man to an operation he may not survive.

Palliative Treatment. The most important palliative measure is very early gastrostomy to stop the mechanical irritation of passing and lodging food and the chemical irritation of fermenting and stagnant food and secretions saturated with oral infections. As Da Costa and Shallow have said, "No surgeon would stretch a cancer." Instead of trying temporary mechanical means to keep the esophagus open, it is better to follow the cardinal rule of surgery to "Let the inoperable cancerous mass alone; put it at rest." The writers who oppose gastrostomy state that it has had, in their hands, a very high operative mortality. These two facts must be taken together. Opposition to gastrostomy means an invariably late operation. Late operations for anything always have a high mortality, but in esophageal cancer late gastrostomy means operation upon a patient moribund from cachexia, inanition, acidosis, and, worst of all, water starvation. Such patients are the worst possible surgical subjects, even for a minor operation. It is no wonder they fail to react. The tissues will not take up water after it is put in the stomach in the worst cases. Up to this time the case has been a medical one. It is now turned over to the surgeon. No wonder the surgeon joins in condemning gastrostomy. Another reason for discrediting gastrostomy is the mental depression that really comes from acidosis. As previously pointed out,[24] gastrostomized patients unless watched will drift into a diet exclusively of raw eggs and meat broths. No one could be happy on such a diet even if swallowed normally. Saliva

is also necessary. If an early gastrostomy is done and the esophagus put at rest with only water by mouth, saliva will go through for a long time.

Radium is useful in some cases, as shown by Fielding O. Lewis,[25] Pancoast, Newcomet, Douglas Quick and others. As pointed out by Quick, overdosage must be carefully avoided.

Roentgen-ray. In our experience, in inoperable cases, patients will live longest under a combination of early gastrostomy, a varied, well balanced diet by tube, plenty of water by mouth and deep roentgen-ray treatment. We have seen objective evidence of benefit from the ray in cases treated by Manges, Pancoast Pfahler, Bowen, Cohen, Borzell and others.

Conclusions. 1. It was stated by the author many years ago that the mortality of malignant disease of the esophagus was, at that time, 100 per cent. Notwithstanding the great advances made in the surgery of malignancy elsewhere in the body the ultimate prognosis of esophageal cancer remains the same today.

2. There is every reason to believe, however, that the reason for this is that the surgeons have never had a chance to develop the technic of a curative operation because the diagnosis is never made early.

3. The reason why the diagnosis is never made early is that the textbooks and journal articles give chiefly or exclusively diagnostic methods that *are always negative early* in the disease.

4. When the time comes in which esophagoscopy shall be resorted to promptly on the appearance of certain very vague symptoms there is ample justification for the belief that the surgeon will cure a good percentage of patients.

5. Squamous-celled endoesophageal carcinoma is not an aggressive type of malignancy. On the contrary, it is a mild, slow and, for a long time, purely local process.

6. Under palliative treatment, if the patient is never permitted to be short of an abundance of water and a full allowance of properly balanced food elements, most cases will survive at least two years from the onset of the disease, and some have survived as long as five years. One lived six years.

7. Patients running the gauntlet of late inferential diagnosis, and leading a precarious existence of various degrees of food and water starvation, depressed and acidotic, on a diet of intermittent supplies of raw eggs and meat broths, may not survive more than a year from the probable time of the onset of the disease.

8. The bougie as a diagnostic means is not only dangerous, but it is inconclusive because inferential; and it is always hopelessly late. A cancer must be well advanced before it will stop a bougie. Even fatal cancer of the esophagus may not be obstructive.

9. The bougie as a therapeutic measure hastens death either by perforation or by increasing metastases. As stated by Da Costa

"No surgeon would stretch a cancer." As stated by Shallow "No surgeon would forcibly dilate malignant stricture of the esophagus any more than he would forcibly dilate cancer of the rectum."[33]

10. There are only two means by which an early diagnosis of esophageal malignancy can be made, namely: (1) Roentgen-ray examination, and (2) esophagoscopy. All other means are late, inconclusive, and some of them dangerous.

11. By esophagoscopy endoesophageal cancer can be diagnosticated not only early, but with the absolute certainty essential to getting the consent of a comparatively well man to an operation he may not survive.

12. Endoesophageal cancer can be diagnosticated just as early, just as quickly and just as certainly as cancer of the cervix if an opportunity for esophagoscopy is afforded early.

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PULMONARY NEOPLASM: A CLINICAL STUDY OF THREE CASES.

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Introduction. The accumulation of case reports both in hospital statistics and in the medical literature of new growths of the lungs is evidence of its frequency. Up to a few years ago lung neoplasm was considered to be one of the rarer medical diseases. The introduction of the roentgen-ray, however, has brought to light many cases which would otherwise have been missed. More recently the bronchoscope has come into more general use and has helped to discover neoplasm of the larger bronchi. The newer agents may enable us to turn these cases over to the surgeon or the roentgenotherapeutist early enough to remove them from the realm of the hopelessly incurable.

This study is based on 3 cases of lung tumor which presented totally different clinical pictures. The object of this report is to emphasize the difficulties of early diagnosis and the importance of thorough physical and laboratory investigation.

Historical. Morgagni,[1] in 1708, was probably the first to mention cancer of the lung. He mentions an autopsy where ulcus cancrosum was found in the lung. Bayle,[2] in 1810, describes 3 cases of phthisis cancereuse, and Laennec,[3] in 1818, speaks of encephaloid tumor of the lung. Stokes,[4] in 1842, describes several varieties of cancer, and Eberman,[5] in 1857, collected 72 cases. The more important contributions to the subject, however, appeared only after cellular pathology was studied and understood. The

earliest microscopical investigations were made by Langhans,[6] in 1871, and Marchiafava,[7] in 1873. Subsequently many noteworthy contributions were made, and a number of original papers and reviews were published. Reinhard,[8] in 1878, collected 27 cases; Wolf,[9] 31 cases in 1895; Paessler,[10] 74 cases in 1896; Sehrt,[11] 177 cases in 1904. In this country Adler[12] collected 464 cases in 1912, and Scott and Forman[13] reported 120 additional cases in 1916. Since then, and especially following the influenza epidemic, many more cases are to be found in the literature.

Frequency. Primary malignancy of the lung is said to be present in about 1 per cent of all cancers, and about one-third of 1 per cent of all necropsies (according to Ewing[14] and Adler[12]). Males are more often afflicted than females, and no age is exempt. McAldowie[15] reported a case of lung tumor in an infant aged five and a half months. The greatest number of cases, however, occur between forty and seventy years of age—over 80 per cent in Adler's series. The right lung is more commonly involved than the left.

Etiology. The etiology is not known. Tuberculosis, anthracosis, chronic bronchitis, interstitial pneumonia, fibrosis, influenza and influenza-pneumonia are mentioned as possible causative factors by various authors. Manifestly no cause can be definitely established for this form of malignancy until the cause for malignancy in general is found.

Anatomy and Pathology. Both bronchi and lungs are developed from an infolding of the primitive esophagus. These consist of simple tubes lined by a double layer of epithelium, which later becomes differentiated into three distinct kinds of epithelial tissue. In the fully developed fetus the trachea and larger bronchi are lined by three layers of epithelium, an outer cylindrical-cell or goblet-cell layer, a middle layer of spindle-shaped cells and an inner layer of wedge-shaped cells resting on a basement membrane. Mucous glands are found throughout the bronchial tree being situated in the submucosa and are lined by a single layer of goblet cells. The mucous membrane of the smaller bronchi retains its ciliated columnar character, but consists of a single layer of cells gradually merging into flat pavement epithelium in the alveoli. Thus it is clear that carcinoma of the lung may arise from any of these structures, bronchial epithelium, mucous gland epithelium and alveolar epithelium.

The lymphatics of the lungs are of two kinds—deep and superficial (Miller[16]). The deep lymphatics are peribronchial and perivascular and anastomose at points of division of the bronchi forming plexuses. These lymphatics become sparer as the smaller bronchioles are approached, there being none in the alveolar wall. The peripheral lymphatics are distributed over the pleura, forming a fairly dense plexus and anastomose with the deep lymphatics as they follow the pleural veins. The normal flow in both these sets of lymphatics is toward the hilum.

Classification. Carcinoma of the lungs and bronchi may be classified according to gross anatomy, histology or histogenesis. Ewing's[14] classification based on histogenesis is followed by most authors, three types being distinguished: (1) Tumor arising from the mucous membrane of the bronchi; (2) tumors arising from mucous gland of the bronchi; (3) tumors arising from alveolar epithelium.

To be sure, in advanced cases it is often impossible to determine from where the original tumor arose. The clinical history, together with the roentgen-ray examination, are at times of indispensable value in establishing the origin of a given tumor. Generally carcinomata of the bronchial epithelium follows along the walls of the bronchi, at times filling the lumen with papillary projections. In some cases necrosis occurs in the superficial tissue, leading to excavation and bronchiectasis. The surrounding pulmonary tissue (alveoli) becomes involved later, but not as uniformally nor as completely as in tumor arising from the pulmonary alveoli. Carcinoma arising from mucous glands sometimes produce characteristic tumors possessing many goblet cells. They are usually limited to the bronchial wall, the lining epithelium of the bronchi remaining intact and stenosis rather than dilatation of the bronchi is the rule. Microscopically these tumors may contain numerous secreting or goblet cells. Carcinoma arising from pulmonary alveoli may be diffuse or nodular, and necrosis is a prominent feature. In their growth they produce either complete or partial filling of the alveoli with cuboidal, cylindrical or flat cells. Squamous-cell tumors, however, may also arise in the bronchi. According to histological appearance, three types are described cylindrical-cell tumors, polymorphous-cell tumors and squamous-cell tumors. Some use a purely clinical classification based on whether or not the tumor in the lung is local, diffuse or general. It is local when it involves but a small area of lung; diffuse, when it affects a fairly large portion of pulmonary tissue, usually extending into other lobes; lastly, it is generalized as when there are metastases outside the lungs.

Metastasis. Metastases of lung tumor are commonly widespread. In Adler's[12] series the bronchial lymph nodes were involved in 31 per cent of the cases, the mediastinal nodes in 12 per cent, cervical lymph nodes in 6 per cent and the tracheal lymph nodes in 7 per cent of the cases (50 per cent for all lymph nodes). The liver was involved in 26 per cent, the pleura in 13 per cent, kidney in 15 per cent, brain in 13 per cent, heart and pericardium in 18 per cent, adrenals in 10 per cent and the bones in 15 per cent of the cases. In order of the frequency they are: (1) Regional lymph nodes; (2) liver; (3) heart and pericardium; (4) kidneys; (5) abdominal lymph nodes; (6) pleura; (7) brain; (8) bones, where it may be widespread ribs, spine, skull and sternum are involved in the

order named. I cannot find any figures as to the frequency with which inguinal and axillary glands are involved. Approximately 25 per cent of the cases show no metastases at autopsy.

Case Reports. CASE I.—Hospital No. 42092. A male, aged forty years, who was admitted to the Lebanon Hospital, October 4, 1923, with the following complaints: Pain and swelling of small joints of hands and feet, fever and headache, and cough.

About four months prior to admission pain, swelling, redness and stiffness of hands and feet appeared. At the same time, he had headaches, some general weakness, and loss of appetite. Loss of sexual power and constipation became manifest within two weeks before admission, and he sought admission chiefly because of pain in hands and feet and loss of sexual power. The patient did not think that he had lost weight.

Physical Examination. General appearance was that of a fairly well developed, but anemic looking, man. The head was negative. The neck showed fairly large masses of glands in both supraclavicular regions; there was considerable edema about the tissues at the base of the neck. There was no evidence of inflammation about these supraclavicular masses.

The lungs showed diminished expansion in the right side, with flatness in the upper two-thirds of the right lung, both anteriorly and posteriorly, and dulness at the base. The breathing was distant bronchial, with a distinct cavernous quality to the expiration. At the left apex there was dulness, and the breath sounds were distant bronchial. There were no rales heard. The abdomen was negative. The extremities showed the joints of both hands, and feet were red, tender and stiff and swollen. This was especially well marked at the metacarpophalangeal joints. The distal phalanges were thickened and showed the changes usually associated with pulmonary osteoarthropathy. The reflexes were normal.

The temperature was 101° F.; respiration, 24; pulse, 100; weight, 135 pounds; blood pressure, 106/36.

Laboratory examination showed: Blood: Hemoglobin, 68 per cent; red blood cells, 3,600,000; leukocytes, 13,000; polymorphonuclears, 80 per cent; lymphocytes, 20 per cent. The blood Wassermann, sputum, stool and urine were negative.

The roentgen-ray showed a dense irregular shadow occupying the upper two-thirds of the right lung, obliterating all the marking. This could either be an effusion or a neoplasm. The pathological report on a small supraclavicular node removed soon after admission was adenocarcinoma.

Clinical Course. While under observation in the hospital the temperature ranged between 99.5° and 101.5° F. Weakness and anemia became marked, and loss of weight was very noticeable.

Enlarged axillary glands appeared about October 12, first on the left side and then on the right. These persisted and became larger. The cough became more persistent and productive; his appetite became very poor and his joint pains did not clear up. He lost ground steadily, and on November 2, 1923, his family removed him to another institution against our advice, where he died, several hours after admission. There, an incomplete necropsy showed, in addition to an extensive right lung and pleural involvement with adenocarcinoma, the presence of a considerable sanguine purulent effusion into the right pleural cavity.

CASE II.—No. 85663. B. S., a male, aged sixty-seven years, was admitted, November 7, 1923. He was discharged, November 28, 1923, with a negative family history and a negative previous history.

The patient came into the Lebanon Hospital, complaining of cough and dyspnea, hemoptysis, loss of weight and weakness, which began about three months ago with a cold in nose and throat, lasting three days. The cough developed soon after the head cold, and was productive of a whitish sputum. There was some pain in the left chest and moderate dyspnea about the same time. The cough was not distressing until about four days before admission, when sputum was blood-streaked and remained so up to admission. Dyspnea was very marked by now. Patient stated that he lost 30 pounds in weight since onset of cough and dyspnea.

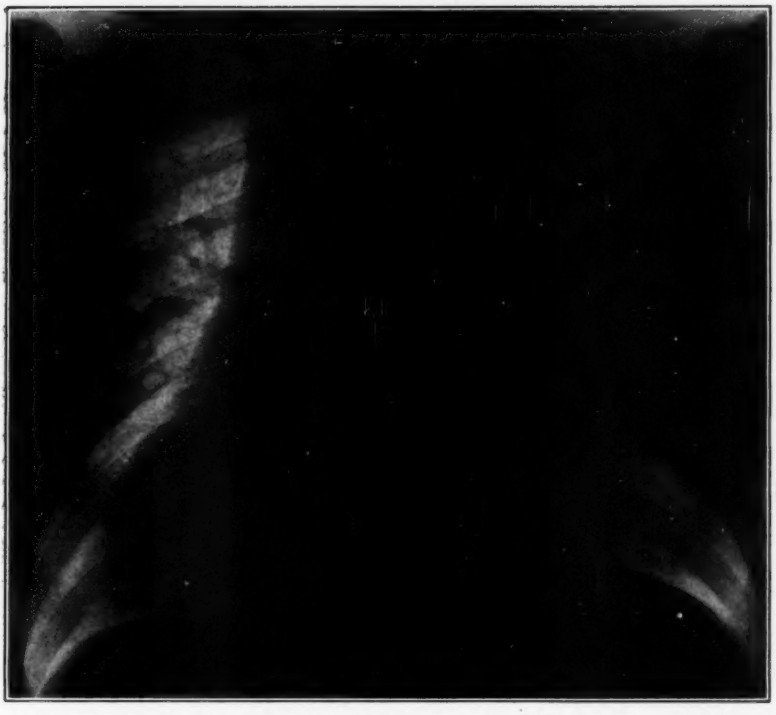
Physical Examination. This showed an emaciated and weak-looking old man, sitting up with an effort and breathing with difficulty.

The chest showed retraction of supraclavicular and infraclavicular as well as intercostal spaces. This was more pronounced on the left side.

Over the entire left chest expansion, fremitus and the breath sounds were very much diminished. The breath sounds, however, were of a distinct cavernous quality, best heard with the naked ear. The percussion note was flat on the left side from the apex downward, except at the very base where it was dull. The right side showed exaggerated breath sounds, with prolonged expiration throughout. There were a few scattered rales over the right base. The rest of the examination was essentially negative.

The temperature was 101.2° F. on admission, but soon became subfebrile, and during the second and third week of the hospital stay it was fairly normal, even though clinically the patient was much worse.

Laboratory Examination. Blood: Hemoglobin, 68 per cent; red blood cells, 3,500,000; leukocytes, 10,500; polymorphonuclears, 82 per cent; lymphocytes, 18 per cent. The blood Wassermann, sputum and urine were negative; blood chemistry was normal;



CASE. I.—Massive involvement of right lung, with patient never complaining of any symptoms referable to respecting system. The glands in both supraclavicular region when markedly enlarged and patient had marked osteoarthropathy.

CASE II.—Diffuse involvement of left side and nodular infiltration on right side with rapidly progressive course.

CASE III.—Hilus involvement with onset of pain in gluteal region.

blood-pressure, 130/70; phenol sulphonephthalein test: 13 per cent first hour and 12 per cent second hour.

Roentgenogram: Dense shadow involving whole left pulmonary field. The density is less in the apical region. There were numerous miliary infiltrations studding the upper two-thirds of the right lung, becoming conglomerate along the middle third about hilum. The trachea is pulled to the left.

Conclusion. A probable new growth in the left lung, with miliary metastasis in the right lung.

Clinical Course. He grew perceptibly worse insofar as his dyspnea increased; cyanosis became permanent. He developed periods of orthopnea. His sputum was profuse and at times blood-tinged. It was repeatedly negative for tuberculosis. He left the hospital on his own responsibility, November 28, 1923, in rather poor shape and died three weeks later.

CASE III.—M. D., a male, aged forty-nine years, was admitted to the Lebanon Hospital, November 26, and was discharged, December 12, 1923.

The family and previous history was negative. He was admitted complaining of pain in the left buttock and the left leg and slight cough. Four weeks before admission he was suddenly seized with pain in the right iliac region and in the right side of the abdomen. Soon thereafter he began to have pain over right lower costal region. The pain was in the nature of an ache, continuous, but aggravated on motion and worse at night, causing loss of sleep, and only relieved by narcotics. This lasted about ten days, when the pain in the leg and abdomen gradually let up, but the pain over the lower left chest became more intense. About this time a cough appeared, and following the appearance of the cough he developed pain in the left leg, especially in the mid-tibial region which was tender. This left-leg pain was quite severe, and persisted up to admission. During the month preceding admission he lost his appetite, became constipated, had an occasional night-sweat and some pain on urination. The patient did not think that he had lost weight.

Physical Examination. The patient was a pale and moderately emacited man who was more or less apathetic, as if in pain. The head, neck and chest showed nothing abnormal. There was some tenderness in the right upper abdomen and lower costal area (tenth and eleventh ribs). This tenderness appeared to be rather superficial, unlike the pain due to involvement of an abdominal viscus. Deep pressure over the ribs, however, caused exquisite tenderness. There was also some tenderness over the vertebral spines from the first to the sixth dorsal spine and over the mid-tibial region. The rest of the examination, including a routine neurological examination, showed no other abnormalities.

The temperature on admission was 99° F. and rose to 101° F. soon afterward, and during observation the temperature varied between 99° and 102.4° F.

Laboratory Findings. The blood showed a moderate anemia; the urine showed a trace of albumin with an occasional hyalin cast. The blood chemistry was normal. The Wassermann on the blood was negative, and the spinal fluid Wassermann was weakly positive. The stomach content after an Ewald meal was normal.

At this junction no diagnosis was ventured, and it was decided to resort to roentgen-ray study of the gastro-intestinal tract and the osseous system. To our surprise, while studying the ribs, on December 1, 1923, a dense irregular shadow was seen to occupy the region of the right hilum infiltrating the adjacent pulmonary tissue. There was no abnormality seen in any of the bones studied (tibia, iliacs, spine and ribs). The roentgenologist (Dr. J. Bower) concludes that there was definite evidence of primary neoplasm in the lung.

Peculiarly enough, even after the roentgen-ray evidence of right-lung involvement, the clinical examination yielded no physical signs. About a week afterward, however, an area of diminished breathing just above the right base posteriorly extending from the spine to the axilla was recognized. Dulness appeared over the same area about the middle of December, six weeks after the onset of illness. About this time a mass was felt in the right upper quadrant, which was thought to be possibly due to metastatic involvement of the liver. A roentgen-ray examination of the iliac region this time showed some areas of rarefaction, probably due to metastasis.

While under observation in the hospital the patient developed prolapse of the rectum, causing him a great deal of distress. He lost ground for a while and then remained stationary, except for the cough which was more or less progressive. He also lost considerable weight. On December 19, 1923, he was removed to another institution for deep roentgen-ray and radium therapy. He was heard from about four months later, when his condition was said to have somewhat improved under treatment.

Discussion. A perusal of the above clinical histories leads one to the belief that pulmonary neoplasm is not always manifested early by symptoms referable to the lung. In but one of the cases (Case II) did the patient complain of cough early in the disease. In another case the pain due to metastasis evidently appeared much before one suspected the lung affection. These facts forcibly emphasize the importance of complete clinical and laboratory investigations, when symptoms and signs are not explicable on an obvious basis. To be sure, a diagnosis of pulmonary neoplasm may not be made on insufficient data, but suspect it one may, and in order to rule it out will require complete laboratory and clinical study.

The role of infection, and more particularly influenza with the resultant epithelial proliferation and atypical metaplasia as a possible source of irritation, is mentioned and stressed by many authors. Moise,[17] in a comprehensive study of 5 cases, is inclined to that belief, and Winteritz and McNamara,[18] both from a study of the pathology of influenza and from experimental data, are led to the same view. Surely there is an evident increase in the number of cases of lung tumor in the past five or six years. However, fascinating as theorizing about the subject as to the genesis of tumor of the lung may be, it must be admitted that the evidence so far adduced indicating influenza, even as a contributary cause, is but circumstantial in nature, and can therefore not be regarded as convincing from a scientific standpoint. For the incidence of cancer elsewhere, which is also admittedly increasing according to mortality tables and reports from life insurance sources, is more easily explained on a basis of better diagnosis, and more correct death reports in general, rather than on a basis of some particular phenomenon, such as the influenza epidemic. Further studies along experimental lines, once the true etiology of influenza is found, may prove more fruitful. At present one can but guess at the cause of cancer anywhere in the body.

Summary. A report of 3 cases of primary pulmonary neoplasm is presented, together with a discussion of the increased frequency of this disorder.

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INTERMITTENT COMPLETE HEART-BLOCK AND VENTRICULAR STANDSTILL.

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The observation of a patient who at times had complete heart-block, with Adams-Stokes attacks due to ventricular stoppage, and at other times a normal heart beat with a normal auriculoventricular conduction time, seems worthy of reporting. Especially is this so since we were able to secure electrocardiographical records of the cardiac mechanism preceding and following the attacks. Moreover, the occurrence of intermittent complete heart-block and syncope, with normal conduction between attacks, has been recorded so rarely that Carter and Dieuaide,[1] in describing a case of their own, collected only eight definite instances in the literature. The case which we wish to report corroborates certain of the physiological facts associated with the Adams-Stokes syndrome, and illustrates in a striking manner the effect of digitalis in precipitating these syncopal attacks, in the presence of a block already complete.

Case Report. S. B., aged fifty-nine years, white, occupation a checker, was admitted to the First Medical Division of the New York Hospital, the service of Dr. Lewis A. Conner, on December 23, 1919, complaining of weakness, dizziness and fainting spells.

The family history was negative, and the patient recalled no infectious diseases, except gonorrhea without complications. In particular, there was absence of cardiorespiratory symptoms of disease.

The onset of the present illness was two weeks before admission, with weakness and palpitation. Two or three times a day fainting spells began to occur, with loss of consciousness for periods of two to three minutes. Such attacks were preceded by weakness and dizziness, and the patient found if he lay down at the beginning unconsciousness did not ensue.

Physical examination on admission disclosed a well developed and well nourished man, lying in bed without dyspnea. There was slight cyanosis of the lips and face. The jugular veins were distended, and their pulse rate was rapid, 100 per minute. The apex rate was 26, with a regular rhythm. Relative cardiac dulness extended 12 cm. to the left in the fifth interspace, and 4 cm. to the right in the fourth interspace. In addition to the heart

sounds, which were normal, there could be heard, inside the apex, faint, short, muffled sounds, sometimes two and sometimes three, in each diastole. There was a faint blowing systolic murmur at the apex. There was no pulse deficit. The peripheral arteries were markedly sclerosed, and the blood pressure was 140/75. The abdominal organs were not felt, there was no edema and pupillary reactions and tendon reflexes were normal. The Wassermann blood test was negative; the blood picture was normal, with hemoglobin 85 per cent, and the urine contained a faint trace of albumin.

Subsequent Record. Three attacks of syncope were observed on the day of admission, with dyspnea and stertor, pallor, loss of consciousness, and general muscular spasticity. No further attacks occurred during the following week, the ventricular rate ranging from 24 to 32 beats, with a rise on two occasions to 44. The treatment during this period was rest in bed, with atropin (gr. $\frac{1}{100}$), by mouth, four times a day.

On December 31, atropin was discontinued and standardized tincture of digitalis was given (0.65 cc per cat unit), 1 dram at 4 P.M., a second dram at 6 P.M. At 12.20 A.M., on January 1, the patient had an attack of dizziness, lasting ten minutes. At 9 A.M. was seen the first syncopal attack since the day of admission. At 11.30 A.M. four attacks occurred during fifteen minutes, and in the afternoon the paroxysms became more numerous, the use of atropin being without effect. The duration of these attacks was usually from thirty to sixty seconds. There would be a period of ventricular asystole of from six to twenty seconds, then the fit, with the gasping for breath, agonal expression, rolling of the eyes, extreme pallor and syncope of varying duration, followed by return of the pulse, with flushing and sweating. During one series of frequent attacks the radial pulse would come back at a rate of about 72, would suddenly cease, a fresh spasm ensue, and so on quite continuously until the reëstablishment of a ventricular rate of 20 to 24 per minute. The blood pressure on January 2 was 144/70.

Another dram of tincture of digitalis was given on January 3. The attacks diminished in frequency and ceased on January 5. On January 6 an electrocardiogram showed 2 to 1 rhythm to be present. Right vagus pressure caused an increase of this block to a higher grade. There was a slight attack on January 7. The pulse-rate rose to 60 to 64 beats per minute at the wrist on January 11, and a record on January 16 showed that normal conduction and rhythm were present. The blood pressure was 150/70. On January 24 the patient was discharged with normal rhythm and free from symptoms.

After working without incident for nearly five months the patient, on June 19, had two short attacks, marked by dizziness, weakness and "flushing in the fingers," without loss of consciousness. He

came into the hospital on June 24, with a ventricular rate of 42 and a venous pulse rate of about 90. On June 29 occurred three slight attacks for the first time since this admission, and notwithstanding a second negative Wassermann test, because of the positive venereal history, 0.2 gm. of neoarsphenamin was given intravenously. Three hours later, at 6 P.M., a series of attacks began which continued throughout the night and the next day, at the rate of two to three an hour. On July 1 the paroxysms were almost continuous, but following the intravenous injection of adrenalin (15 minims, 1 to 1000) the ventricular rate rose to 66, and after two or three short paroxysms they ceased entirely for one and a quarter hours.

On July 2, following adrenalin, the ventricular rate became 66, with a pulse of good quality, and regular. Suddenly the pulse became irregular and almost imperceptible at a rate of about 100. The patient became pale with labored breathing, and the presence of ventricular fibrillation was suggested by the irregular faint heart sounds. The cessation of the pulse cut short this condition, a typical convulsive attack occurred, and these continued until the patient became permanently unconscious and died, July 3.

Necropsy. At the necropsy, performed by Dr. R. G. Stillman, the heart, which weighed 425 gm., was found firmly contracted. The left auricle was dilated and was lined by an endocardium thickened, white and smooth. The segments of the mitral valve were thickened and contracted, and the chordæ tendineæ were shortened. There was a calcified ring about the left auriculoventricular orifice for about three-quarters of its circumference. "The muscle is firm and presents no focal lesions, but is rather more yellowish in color than normal, and appears as though there were some increase of fibrous tissue in it." The aorta was not enlarged. The coronary and larger arteries were moderately atheromatous, but there was no narrowing of the lumina of the former.

The conduction system showed no gross abnormality, though the calcified ring must have lain in close proximity to it. Unfortunately, the conduction system was not examined in serial sections. The sections of ventricular muscle showed no abnormality. It is possible and probable that the calcareous changes around the mitral orifice had involved the bundle.

Electrocardiographical records of this patient were made at intervals from the day of his first admission to shortly before his death. They show complete heart-block and the transition through 2 to 1 rhythm to a state of normal conduction, and later the recurrence of the complete heart-block. Electrocardiograms illustrating these phases are reproduced. Fig. 1, secured on admission, shows complete block with the auricular rate 92, and the ventricular rate 27, per minute. The prolongation of systole to 0.64 second is note-

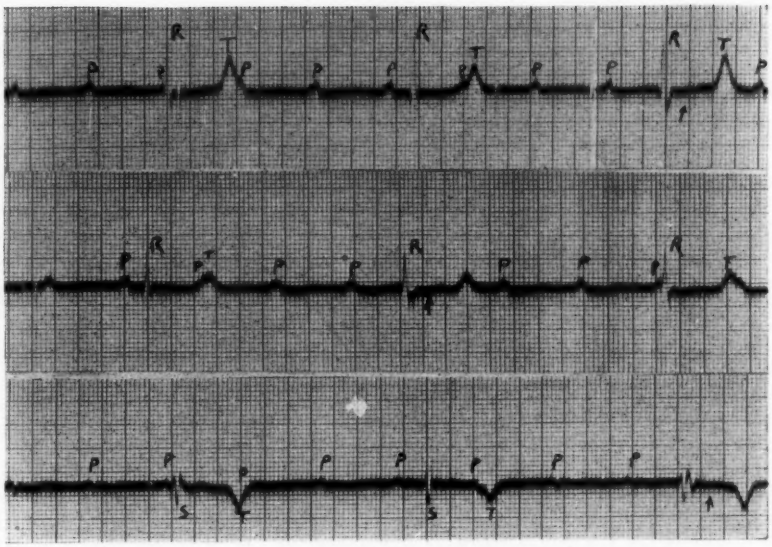

FIG. 1.—Record on admission showing complete heart-block.

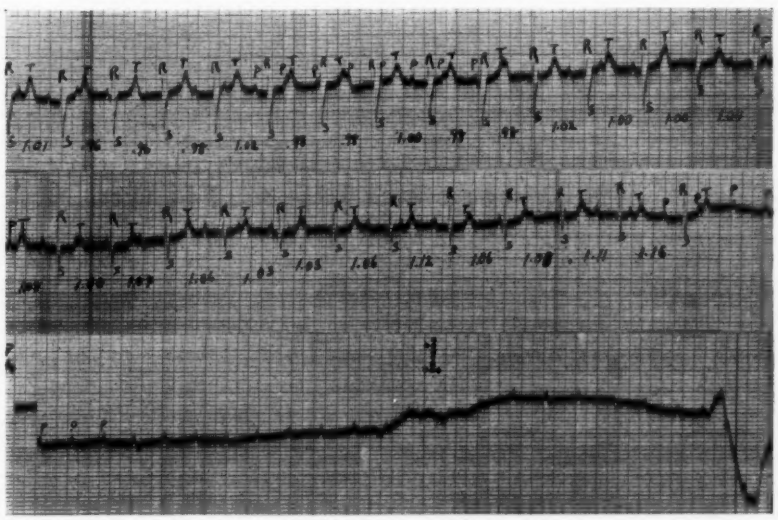

FIG. 2.—Record of January 3 showing paroxysmals of ventricular tachycardia with complete heart-block, followed by ventricular stoppage. This record is by Lead I and the three parts of it are continuous from above downward, overlapping slightly as can be seen. The figures are the duration in seconds of each interventricular interval. The large movements at the end of the record are due to the onset of a convulsion.

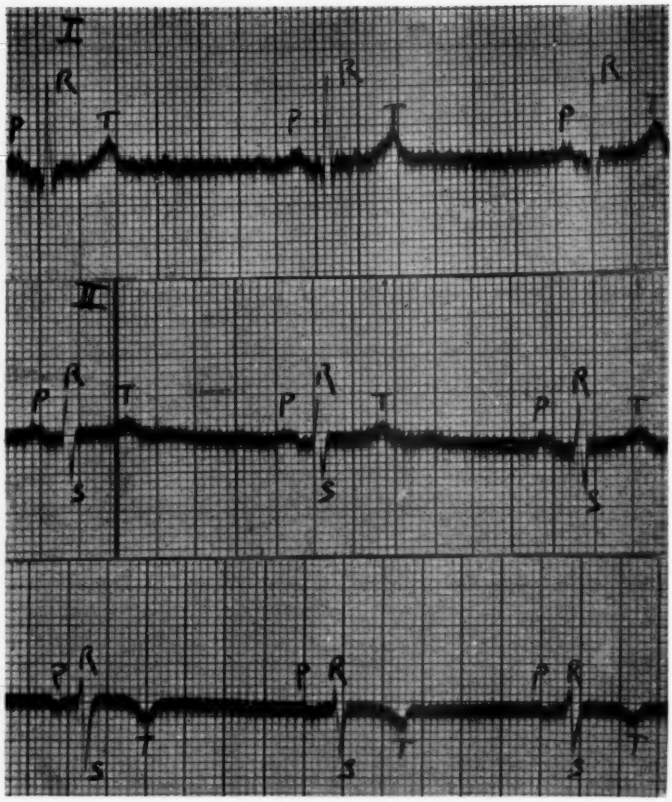

FIG. 3.—Record of January 16 showing normal A–V conduction time, the P–R interval measuring 0.18 second.

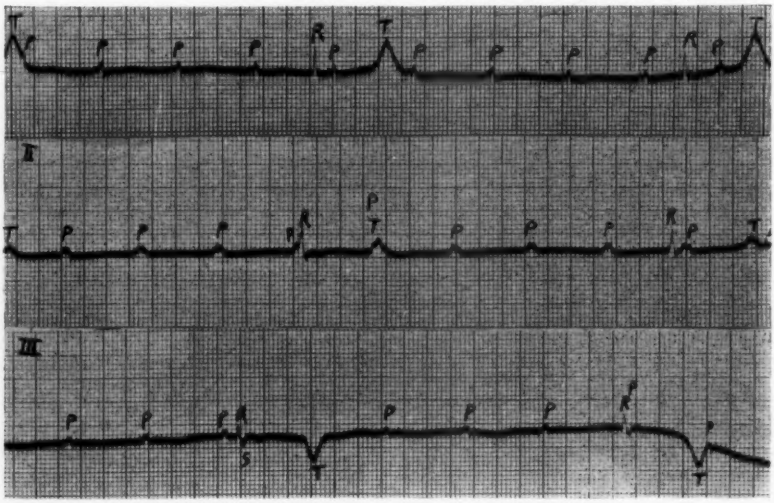

FIG. 4.—Record of January 29 showing complete heart-block with a very slow ventricular rate, about 18 per minute.

worthy, but is common with such slow heart rates. The *Q–R–S* group has a duration of 0.12 second, but the presence of the supraventricular form indicates that the impulse, as is usual with complete heart-block, arises from the *A–V* node or at least from a part of the *A–V* bundle above its branching. During this record the ventricular beat is quite regular, but on January 2 records were obtained with an irregular ventricular action of about 15 to the minute. The pauses between beats were sometimes as long as six or eight seconds and varied irregularly. At the same time, the auricles were regular at 94 per minute. The ventricular waves, as in Fig. 1, showed an origin in the *A–V* node or bundle.

Fig. 2, taken on January 3, when frequent paroxysms were in progress is of particular interest as showing the cardiac mechanism before the attack. The first portion of the record, which is by Lead I, shows ventricular tachycardia. The ventricular rate is 60; the auricular rate is 100. Both chambers are regular in rhythm. At the fourteenth beat there is a change in the form of the ventricular complex. The duration of the *Q–R–S* group diminishes from 0.14 second to 0.12 second and later to 0.1 second, and the form of the waves comes to resemble more nearly the usual complexes of this lead as seen in Fig. 1. Both the *Q–R–S* and the *T* waves are changed. The diastolic interval lengthens irregularly as this change in the form of the waves takes place, and finally, after two still longer pauses, the ventricles cease beating. The gradual decrease in the irritability, along with a change toward the normal in the waves of the ventricular contractions, suggests that the stimulus for the heart beat is changing its location from a point in the (right?) ventricle to a point in the *A–V* bundle above its branching.

This lengthening of the diastolic interval with change in location toward the *A–V* node was observed in the other records of this patient which showed the cessation of the ventricular beat. It would seem that the *A–V* node at this time was unable to maintain a spontaneous beating, and only when the ventricular centers took over the function of stimulus production could the heart beat be maintained. The lowered irritability of the node which caused the slow irregular beating on January 2 had now given way to a complete depression of irritability.

The attacks ceased on January 5, and on January 6 a record showed partial heart-block, the auricular waves being followed alternately by a normal conduction interval (0.16 second) and by a failure of conduction. This 2 to 1 block continued for several days, and Fig. 3, taken on January 16, showed a normal heart beat, 60 per minute, with normal *A–V* conduction time (0.16 second). A change in the *T* wave was seen as might have resulted from the 3 drams of tincture of digitalis which were given on January 1 and 3. It has disappeared in Fig. 3, which shows

ventricular waves like those of Fig. 1, except that there is a more definite left ventricular predominance.

On April 1 the patient returned for a record which was quite similar to Fig. 3 and showed normal conduction.

Fig. 4 was taken on June 29, during his second admission, on the day he began the series of attacks that proved fatal. Complete heart-block is present, the auricular rate being 85 per minute, while the ventricles beat regularly at 19 per minute. The small size of the *Q–R–S* group in all leads of this record is probably due to a poor physiological condition of the muscle. There was no significant difference in blood pressure whether complete heart-block (excluding, of course, the time of attacks) or partial block or normal rhythm was present, and the size of the *T* wave during periods of complete block, compared with its amplitude during normal *A–V* conduction, indicates the more forceful ventricular contraction associated with the slower rate.

Discussion. The clinical interest of this case attaches to the intermittent complete heart-block with normal *A–V* conduction intervening, and to the periods of ventricular standstill, during which the patient exhibited all of the usual sequelæ of such attacks: the sensation of flushes in the fingers and other parts accompanying momentary cessation of the beat; the loss of consciousness which commonly, though not always, occurs when stoppage lasts more than two to three seconds, and finally the epileptiform seizures that supervene after asystolic periods of from fifteen to twenty seconds' duration. In the reported cases there have been wide variations in the duration of standstill before convulsions occur. In the record from our patient taken on January 2, when the ventricular action was very slow and irregular, the waves characteristic of muscular spasticity appeared after six seconds of ventricular stoppage. At the other extreme, in a patient reported by Wiltshire,[2] periods of standstill up to sixty-seven seconds occurred without convulsive movements. The most prolonged duration of ventricular stoppage so far reported was for one hundred and thirty seconds, which was observed in the patient of Stengel,[3] and in this case convulsions occurred.

Of paramount importance is the opportunity to analyze the electrocardiographic records of ventricular stoppage in man, for, naturally these are still rare, though the phenomenon has been recognized for a full century. The polygraphic records that have been secured from time to time have thrown much light on the physiology of ventricular stoppage, but particularly important observations on ventricular standstill in dogs have been made by Erlanger and Hirschfelder[4] in the course of experiments upon the mechanical production of heart-block. Their conclusions were that stoppage could be produced in four ways: (1) By inhibition of the auricles through vagus stimulation, while the conduction

system is intact; (2) in the presence of partial heart-block, by an increase in auricular rate, which produces fatigue of the *A–V* bundle; (3) by a compression of the bundle sufficient to produce complete heart-block; (4) in the presence of total heart-block, by the sudden cessation of fairly rapid rhythmic ventricular stimulation. The underlying cause in each case is the lack of the usual stimulus to contraction, no matter whether this is ventricular or supraventricular. The ventricle then remains in standstill until its dormant pacemaker again begins to function.

In the case here reported the evidence suggests that the ventricular stoppage was due to variations in ventricular rhythmicity. The changes in the form and in the duration of the ventricular complex of the electrocardiogram immediately preceding the periods of ventricular standstill are proof of corresponding changes in the pathways of intraventricular conduction, and, by inference, in the site of origin of the impulses. It is reasonable to suppose that the ventricular tachycardia depressed the irritability of the ventricles and brought about the inactivity of one pace-making center after another until stoppage resulted.

It always demands careful study, however, to properly estimate the importance of these various physiological mechanisms in specific instances of ventricular standstill. In Starling's patient,[5,6] for example, vagus stimulation alone was responsible for the lapses of ventricular beats. Erlanger[7] constantly noted auricular acceleration in his patient immediately before the ventricular silence. In the patient observed by Earnshaw,[8] and by Thayer and Peabody,[9] diminution of ventricular irritability appeared to play the predominant role, though vagus action on the auricles and a partially defective function of the *A–V* bundle were also regarded as factors. In the case reported by Wilson and Robinson,[10] a rapid idioventricular rate and the resulting depression of ventricular irritability, seemed to be the most important factors, but they considered that a disturbance of auriculoventricular conduction was also a factor. An example of a purely mechanical production of heart-block and ventricular standstill is reported by Lewis[11] in a case where engorgement of large blood sinuses in the *A–V* bundle caused the attacks.

It is evident that any of the several mechanisms discussed by Erlanger and Hirschfelder[4] may be operative in different patients, and it will always be a nice study to decide in each case. As Lewis[12] says, "The solution of the problem of the fits of complete heart-block rests with the investigation of the influences which increase or decrease the idioventricular rate," and to this end the information of the electrocardiographical record must be correlated with accurate clinical data.

Summary. A case of intermittent complete auriculoventricular heart-block is reported.

Syncopal attacks during the complete block are found to be due to ventricular standstill, varying from six to twenty seconds' duration. Such attacks followed the administration of digitalis.

The physiological factors bearing on cessation of the ventricular beat are discussed, and it is concluded that in this instance changes in nodal and ventricular rhythmicity appear to be the governing factor in producing standstill, while definite vagus and auricular influences are absent.

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GOITER HEART.

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It is now generally believed that thyrotoxic states, whether induced by exophthalmic goiter or by toxic adenoma, are characterized by an abnormal increase of oxidation in the tissues. This increase of oxidation is what we attempt to measure and to express in terms of basal metabolism. By this increased consumption of oxygen, the patient with Graves disease is on a physiological plane with the normal individual who is doing hard muscular work. Physical exercise increases the consumption of oxygen and elevates metabolism, and the same is true of febrile states. When the tissues require more oxygen, the work of transporting it from the lungs to the tissues falls upon the heart; therefore, other things being equal there is rapid heart action during severe exertion, with pyrexia and, in general, whenever there is an elevated metabolism. Thus considered it becomes evident why abnormal states of metabolism may be accompanied by disorders of heart action, or, if these states be prolonged into chronicity, by actual myocardial degenerations.

The toxic state of hyperthyroidism may be induced by the classical type of exophthalmic goiter, or equally well by the less striking clinical syndrome of adenoma of the thyroid. In fact the two syndromes not rarely merge, one into the other, with a result that cases

of toxic adenoma with exophthalmos are regarded as true exophthalmic goiter. Differentiation is an attempt to harmonize clinical syndromes with anatomical lesions, an attempt which in this instance is often possible; but there are striking exceptions. In essentials the cardiac disorders secondary to exophthalmic goiter are the same as those associated with toxic adenoma. But since the latter disease is apt to develop somewhat later in life the damage to the heart in cases of adenoma is more likely to be serious and permanent than with exophthalmic goiter. Complete irregularity of the pulse is commonly held to be evidence of a grave cardiac lesion, and this may be the case; but this irregularity, even when associated with symptoms which suggest circulatory embarrassment, is hardly a criterion of organic heart disease since a permanent reversion to normal rhythm can so often be induced.

Cases of thyrotoxicosis, of whatsoever causation, are prone to have symptoms suggestive of cardiac disease. Besides the usual tachycardia, these symptoms are palpitation, pain and dyspnea. These symptoms may be present when there is no detectable evidence of cardiac disease—indeed in cases where the subsequent history is of such a character as to exclude cardiac disease. Statistics are of little help in formulating judgment concerning a concrete case; but it is probably conservative to estimate that over half the cases presenting symptoms have no significant organic lesion. There are too, other reasons than symptoms alone which may lead to mistakes in diagnosis. Not infrequently in milder degrees of thyrotoxicosis the apex impulse has a slapping quality and there is a prolongation of the first sound closely resembling a murmur. When these signs accompany symptoms, it is easy to understand why the case may have been regarded as one of mitral stenosis. The error is most likely to occur when the evidences of thyroid disorder are latent and obscure. Sometimes there are signs suggestive of aortic regurgitation. In toxic thyroid states the systolic blood pressure is either normal or slightly elevated while the diastolic is low on account of the vasodilation of the arterioles. This constitutes a high pulse pressure notable in the radial as a pulse of water-hammer or Corrigan type.

There is quite a different syndrome, which on account of the preeminent symptoms being of a vascular character, not infrequently simulates hyperthyroid states. When neurocirculatory asthenia occurs in a young woman who also happens to have an adolescent goiter, the resultant impression is apt to be that of thyroid disease. More or less constant tachycardia, dyspnea on exertion, some tremor; these are the usual symptoms and examination of the heart often reveals a slight thrill, with systolic shock and possibly a prolonged first sound which is almost a murmur. The identical symptoms and signs are often noted in young individuals of somewhat asthenic type and are correctly interpreted as not related to any organic

cardiac disease; but when there is also a visible thyroid enlargement, it seems to prejudice judgment and due weight is not given to conflicting evidence. The subsidence of this tachycardia during sleep is one of the helpful means of differentiation.

The commonest type of cardiac disorder accompanying thyrotoxicosis is auricular fibrillation, detectable on account of the complete irregularity of the pulse. Arrhythmias induced by numerous premature systoles, or by flutter are less frequent. In early cases of exophthalmic goiter there may be periods of auricular fibrillation followed by periods when the pulse reverts to a normal rhythm. In fact it is probable that persistant fibrillation is usually preceded by paroxysmal fibrillation. Now these complete arrhythmias are credited with an omnious significance which is far from correct. While fibrillation of the auricles may be one of the signs of a failing heart, it is equally true that complete irregularity is not incompatible with years of arduous life. But the chief consideration in its relation to thyroid disease is that this type of cardiac disorder increases to a marked degree the danger incident to any operation. For reasons which are not entirely clear, mural thrombi are prone to form in the fibrillating auricles and following operations detached portions of these thrombi occasionally produce embolism and infarctions. This is also a danger if quinidin be carelessly employed.

Why the heart is especially liable to this peculiar arrhythmia in hyperthyroid states is a matter of conjecture largely, probably the low vagus tone which characterizes the primary disorder is an important factor. Whether there is also a lesion of the myocardium which might be a predisposing factor is not definite. There is evidence for such an idea both in the character of the lesions found at autopsy and likewise of the lesions which may be produced in animals by feeding thyroid substance. It is difficult, however, to interpret correctly the lesions found in the human heart in cases of thyrotoxicosis. That the myocardium in such cases presents evidence of degeneration has been noted repeatedly. Fatty degeneration, perivascular round-cell infiltration, sometimes focal necroses, these have all been described. But these are not unusual lesions in various chronic diseases, which occur in middle life and they are perhaps especially common in association with simple, non-toxic goiter. In order to indicate a direct relationship between these lesions and hyperthyroid states, it would be necessary to show that myocardial degenerations of these types are very much more common in cases of thyrotoxicosis than in other cases dying at the same age periods, also it would be necessary to exclude other possible causes for the lesions. There are at present no statistics on this subject. Color of plausibility is given to the conception of myocardial degeneration being produced by thyrotoxicosis by experiments on animals. Perivascular infiltration and focal necroses have been found in animals following periods of feeding thyroid

substance or the injection of thyroxin (Hashimoto, Goodpasture). Possibly quite as important is the observation that the heart of an animal thus treated appears to be more vulnerable to some toxic agents (that is, chloroform) than the normal heart. Perhaps it is not so much the increased activity of the thyroid which affects the injury, but rather that the intoxication produces a condition in the myocardium which predisposes it to injury from minor infections. Should it be possible to demonstrate foci of degeneration in the hearts of persons dead of thyrotoxicosis, this fact would help to explain the predisposition to auricular fibrillation already mentioned. Experimentally, fibrillation is easily produced by faradization of an area in the auricles and the current theory in explanation of fibrillation assumes foci of degeneration in the auricular myocardium.

It has often been noted that the heart in cases of thyrotoxicosis is enlarged. Because there is such an evident demand upon the heart in this disease, it has been assumed that the enlargement is due to hypertrophy. Marine and Lenhart expressed this idea in suggesting that the goiter heart is a result of work hypertrophy. Just what an elevated metabolism means in demand for increased cardiac effort deserves consideration. In thyrotoxic states the increase in basal metabolism is often of such a degree that the patient when at rest is on a physiological plane with a normal person engaged in hard exercise. Physical exercise increases basal metabolism. Elevated metabolism, whether normally induced by physical exertion or abnormally induced by intoxication means increased oxygen consumption. Boas has calculated that in the thyrotoxic patient one-quarter again as much oxygen must be transported from the lungs to the tissues as in a normal person. The chief means for this accomplishment is by increasing the rate of the circulation. The increased minute-volume flow in exophthalmic goiter was demonstrated by Plesch some years ago and he estimated that it amounted to about 50 per cent. This increase is effected apparently largely by rise in heart rate since there is no evidence that the systolic output is augmented. The total bloodflow in thyrotoxic states is roughly proportionate to the metabolism rate, hence an elevated metabolism must increase the work thrown upon the heart. Besides these somewhat mathematical relations, there is the factor of wastage. Plummer and Boothby have shown that the patient with toxic goiter labors under the peculiar handicap that to perform a given amount of work more energy is required than under normal conditions.

It would seem then, in view of these constantly augmented demands on the heart, that ventricular hypertrophy would be an inevitable result. This does seem to happen occasionally but not with any constancy or consistency. Of 21 cases examined postmortem (Wilson) in only 2 did the heart exceed 500 gm. in weight. An increase of 10 per cent over the theoretical normal is not enough to

prove hypertrophy. And there is now a recognized relation between ventricular weight and body weight. Lewis expresses this relation as a ratio and Hermann and F. Wilson determined this ratio in a series of thyrotoxic cases studied postmortem and found an average of 0.00292, which is similar to Lewis's figure for normal. One is forced to conclude then that while some cases may show unquestionable degrees of cardiac hypertrophy, nevertheless hypertrophy is not the inevitable result that might be expected.

The various factors which operate to produce goiter heart are confusing and in some essentials not yet understood. It is, therefore, to be expected that therapeutic measures will be somewhat in debate and that now and then someone questions the usefulness of digitalis; perhaps even holds it to be dangerous. Since the vegetative nervous system in cases of toxic goiter is disordered and the effect of digitalis on the heart is in part produced through the vagus, there will be less prompt response to digitalis in this disease than in cases of purely cardiac disease. Of ill-effects of digitalis I have seen none, and but rarely has it been impossible to restore a normal rhythm in cases of fibrillation. In the last year during which, in addition to digitalis, we have used quinidin in a manner which seems peculiar to our clinic, we have not failed to restore normal rhythm in any case of fibrillation in a goiter heart.

The risk of operation in cases of thyrotoxicosis is appreciably greater when there is auricular fibrillation. On this account especially, it is of great importance to restore a normal rhythm as a part of preoperative treatment. Then too, these sensitive patients seem to be unusually conscious of the turmoil of arrhythmia and so soon as it ceases they at once become more quiet and improve surprisingly.

No measures directed solely to treatment of the cardiac disease are likely to be successful unless combined with methods to improve the general condition of the patient. The first essential is rest, physical and mental. This is necessary in any severe cardiac disorder and is especially demanded in cases of goiter heart. The patient must be kept in bed. Sedatives are usually required, luminal or chloral are preferable to bromides because the latter upset digestion. Sufficient sleep must be secured even if morphin has to be used. The cautious use of iodin is indicated; it is often effective in reducing metabolism in exophthalmic goiter though not invariably, and sometimes in cases of toxic adenoma. When the metabolism does not subside after iodin therapy it may do so with quinin. There are scientific grounds for the use of quinin, though it has never been tested systematically in thyroid disease. In addition to these general measures the first step in attempted control of auricular fibrillation is to effect digitalization. The amount of digitalis required to do this is variable and it may be only roughly estimated as an average of 2 minims of tincture per

pound body weight. Half the theoretical amount may be given as the first dose, the remainder within forty-eight hours, according to Pardee's method. After this, digitalis should not be discontinued though the dose may be decreased, the daily amount must be determined by the pulse rate and evidence of toxic effect. In cases of thyroid disease even when there is no gross evidence of cardiac disorder a careful study of the heart is indicated, and when the electrocardiogram shows the usual characteristic abnormal *T* wave, systematic use of digitalis should be carried out, especially if operation on the thyroid is contemplated.

In some instances when the response to treatment is prompt and the metabolic rate abates considerably, there is a reversion from auricular fibrillation to normal rhythm after the use of digitalis alone. More often, however, this does not occur, at least in our experience which is apt to be with cases of considerable duration before they enter the clinic. It is with this latter group that the treatment with quinidin is so effective. In the first place quinidin cannot be expected to act on a heart which is grossly incompetent; and it is possible in such cases that its influence becomes dangerous. So long as there is edema, passive congestion of the lungs or kidneys, or a pulse deficit, quinidin, in my opinion, is contraindicated. It is contraindicated also if there is fever.

Before using quinidin it is necessary to have the patient well under the influence of digitalis. It is not always possible in cases of toxic goiter to secure the slow pulse of about seventy per minute which we strive for in cases of fibrillation due to purely cardiac disorders, but a considerable slowing is usually attainable. Whether the interesting theory advanced by Riecker of our staff is correct or not, it is certainly true that quinidin acts best on the digitalized heart. When quinidin is administered the dose should be 0.4 or 0.5 gm. every four hours, day and night. Often there is reversion to normal rhythm within twenty-four hours, then the dose may be gradually decreased. If there is no effect after a day, the dose should be doubled for thirty-six hours. I have never seen any untoward effect other than slight tinnitus and mild diarrhea. When a restoration of rhythm has been secured, quinidin should not be discontinued at once, though the dose may be reduced considerably. The drug is eliminated rapidly and it is questionable, of course, how much influence 0.2 gm. twice daily has in maintaining normal rhythm. But it has been my impression that the small dose along with the continued use of digitalis prevented further fibrillation. At least there has been a surprising success with the method, and in several instances of thyrotoxicosis fibrillation has been associated with signs of severe cardiac incompetence—dyspnea, edema and evidence of passive congestion of the kidneys. Finally one important factor cannot be disregarded, namely, time. It is sometimes necessary to treat the patient for weeks as a cardiac case before surgical

measures can be entertained; but by so doing some very gratifying results have been secured.

Summary. CONCLUSIONS. Cardiac symptoms associated with thyroid disease are of common, even usual occurrence, but these symptoms may be of pronounced severity without detectable evidence of heart disease. The socalled cardiac deaths which follow operation are seldom due to heart failure but more often to vascular failure; that is to say, there is, in these cases, a vasomotor paralysis and a widening of the peripheral vascular field notable by a sharp drop in the diastolic blood pressure, a condition similar to shock.

The commonest type of disorder referable to the heart in thyrotoxicosis is auricular fibrillation. Whether this arrhythmia is due to lesions in the myocardium or to nervous influences is not yet known. Lesions in the myocardium have been described in cases of thyroid disease and they have been experimentally induced in animals, but these lesions are not found in every case.

Heart block and auricular flutter are of exceptional occurrence and probably denote serious myocardial degeneration.

It is important to control auricular fibrillation, especially if operation be contemplated, since the mortality in cases with fibrillation is higher than in controlled cases.

A reversion to normal rhythm may be usually secured by proper treatment, which includes rest, digitalis and quinidin.

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EVENTRATION OF THE DIAPHRAGM, WITH A REPORT OF A CASE EMPHASIZING THE VALUE OF THE MOVEMENTS OF THE COSTAL MARGINS IN DIAGNOSIS.

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THE object of this paper is to report a case of eventration of the diaphragm, to discuss the literature in relation to the same and to call special attention to the aid given by the study of the movements of the costal margins in diagnosis.

Case Report. Mr. R., a chemist, aged thirty-seven years, complained chiefly of indigestion and insomnia. His father died of

apoplexy at the age of fifty-eight years; his mother died at the age of forty-seven years, following an operation for the removal of a tumor of the abdomen. Two brothers died in infancy, and two brothers and one sister are living and well. He has been married four years, and is the father of two children. His wife is living and well. He had the usual diseases of childhood, including scarlet fever, and suffered from frequent attacks of tonsillitis during 1922. There is no other history of infection, and venereal disease is denied.

The patient denies the use of alcohol to excess. He smokes two cigarettes a day. He has three regular meals a day, and does not eat between meals or on retiring. Sweets are not taken to excess. Four glasses of water, two cups of coffee and one cup of tea are taken daily. He voids four or five times a day, but has no nycturia, dysuria or hematuria. His sexual life is normal. For the past eleven years at various times he has had indigestion, preceded by constipation and characterized by discomfort in the abdomen just above the umbilicus, which occurred from fifteen minutes to one hour after meals. This discomfort, which was not painful, but seemed due to pressure, was followed by a diarrhea of two or three movements of a soft consistency without blood or mucus. These attacks occurred once or twice a month, and appeared to be related to an increase in his mental responsibilities or if he worried.

At no time was there vomiting, and the attack usually disappeared spontaneously. His appetite remained good, there was no loss of weight or jaundice, and during the interval he was free from discomfort. He has always been considered nervous, in that trivial things worried him, and any increased responsibility made him more irritable. At these times he suffered from depression, melancholia and insomnia; otherwise his sleep was undisturbed. There has been no disturbance of the special senses, numbness of the extremities, or headaches. At no time has there been any cough. Since childhood he has been conscious of dyspnea, so that he never was able to do what other boys did without shortness of breath and exhaustion. The dyspnea has not increased in severity and is brought on by exertion. He considers the discomfort in the abdomen, the increased irritability and the insomnia, all definitely related to each other.

Physical examination showed a pale and somewhat emaciated man, weighing 132½ pounds, and 68¾ inches tall. He had a good growth of hair on the scalp, eyebrows, chest, abdomen, axilla, forearms and legs. There was a small area of pigmentation on the right shoulder; the skin was otherwise clear. The thyroid was not enlarged. The tonsils were buried; considerable secretion was expressed from the left one. The tongue and the sinuses upon transillumination were normal, and the teeth were in good condition. There was no exophthalmos, and no von Graefe, Stellwag or

Moebius signs. The abdomen was normal to inspection and palpation. The chest was of the flat type, and the left supraclavicular and infraclavicular regions were more sunken than the right. Anteriorly above the expansion was equal on both sides. The upper and lower costal margins on the left side moved outwardly more than the right side. The right side was normal to percussion and auscultation anteriorly and posteriorly. The left side on percussion was found high pitched posteriorly from the fourth dorsal vertebra to the top. At the left base modified tympany was obtained. There was found excursion of the left diaphragm from the eighth to the ninth dorsal vertebra on deep inspiration. Tactile fremitus was retained. The breath sounds were normal and no rales were heard. The following day the same movements of the costal margins were found; percussion of the left base, however, revealed dulness instead of tympany, with diminished breath sounds. In the cardiovascular system the brachial arteries were soft, straight and smooth. The radials were equal, full, compressible and regular. Blood pressure on both arms was 108/70. The apex-beat was found in the fifth interspace, 9½ cm. from the midsternal line. No increased dulness at the base or to the right of the sternum. The heart sounds were normal. No adventitious sounds were heard.

Neurological examination was negative, except that the patella and Achilles reflexes were exaggerated but equal on both sides. The rectal examination revealed a relaxed sphincter, no hemorrhoids were seen. The prostate was smooth and no apparent enlargement was found.

Laboratory Evidence. Urine examination (twenty-four-hour specimen, 35 ounces). Amber and clear; specific gravity, 1026; acidity, 52; albumin, sugar and ketones, negative; indican, a trace. On microscopical examination a few pus cells and epithelial cells were seen. Lumbar puncture: The spinal fluid was clear and not under increased pressure. Cell count, 3; sugar, slight reduction; globulin, negative; Wassermann test, negative.

Blood Examination. Hemoglobin, 110 (Dare); erythrocytes, 5,030,000; color index, 1; leukocytes, 7060; neutrophiles, 54 per cent; eosinophiles, 1 per cent; small lymphocytes, 43 per cent; large lymphocytes, 2 per cent. The Wassermann test on the blood serum was negative. Blood chemistry was normal.

Gastric Analysis. Examination of the fasting and test-meal was normal. More details relative to the blood chemistry findings and gastric analysis will be furnished by the writer if desired.

Roentgen-ray Evidence. By fluoroscopic examination of the chest the diaphragm on the left side was seen to move upward with inspiration and downward with expiration. The smooth curved line of the diaphragm was seen to occupy a higher level on the left side than on the right. Barium series revealed a high position

of the cardiac end of the stomach within the chest, also a high fluid level in the stomach was seen. The splenic flexure was found to extend well up into the chest both in the twenty-four-hour observation and the barium enema. The roentgenographical conclusions were eventration of the left diaphragm, high position of the cardiac end of the stomach, displacement of splenic flexure within the chest, paradoxical respiration.

Discussion. In recent years the study of the diaphragm has aroused considerable interest, because it is being constantly appreciated that the diaphragm in its relation to thoracic and abdominal diseases plays a very important part.

Eventration and hernia of the diaphragm were formerly considered to be of purely pathological interest, but since the use of the roentgen-ray in diagnosis there has been a decided increase in the number of these cases reported. Statistics of the last five years, in comparison with those of the last fifty years, will illustrate forcibly this point. However, it is well to remember that these conditions were recognized many years prior to the use of the roentgen-ray for diagnosis.

Historical. The credit is given to Jean Louis Petit, a brilliant French surgeon, for having reported the first case of eventration of the diaphragm. This is mentioned as occurring in 1790, but could not be true because Petit died in 1750. Morrison, of England, rightly calls attention to this fact. He accounts for the error by the statement that the third edition of Petit's writings appeared in 1790. Petit had previously seen at autopsy a case of hernia of the diaphragm. It was found that the stomach, colon and part of the omentum had passed through a defect in the dorsal portion of the diaphragm. There was no hernial sac. Later he observed another case in which there was found at postmortem a small gourd, or tumor, which occupied the left chest. It consisted of stomach and colon enclosed in a hernial sac, and was covered by peritoneum, diaphragm and pleura. He considered the condition to be of congenital origin, and clearly a different one from that which he had observed in relation to the hernia. He, therefore, called the condition "eventratio diaphragmatica."

However, Cruveilhier, in 1849, was the first to describe accurately the condition. Confusion has arisen since then because various writers have used different terms, such as high diaphragm, relaxed diaphragm, insufficiency of the diaphragm, to designate this condition. None of these terms, including eventration, accurately expresses the condition present, but eventration expresses it as well as any. Cruveilhier used the term eventration to designate a high diaphragm, with displacement of the organs of the abdomen into the chest, the walls of the diaphragm thinned, but intact, and with no defect in its continuity. This finding differentiates eventration from hernia of the diaphragm in which a defect or slit in

the diaphragm occurs. Unfortunately this pathological differentiation is not fully recognized, and a study of the literature impresses one with the fact that many writers use the term eventration when they actually have a case of hernia and *vice versa*.

Eppinger, in 1911, compared the relative frequency of eventration and hernia as follows:

	Right side.	Left side.
Hernia vera	21	53
Hernia spuria	34	527
Eventration	2	15

The total cases of eventration were 17, and the total cases of hernia were 635. The ratio of eventration to hernia was 1 to 37.

In 1916 Bayne-Jones described a case of eventration of the right side. He stated that a number of reported cases of eventration had increased to 45, with a corresponding increase in the number of cases of hernia.

Korns, in 1921, expressed considerable doubt as to the accuracy of some of the reported cases of eventration of the diaphragm, and showed by a critical analysis of the reported cases that some were not cases of eventration. He, therefore, summarized the condition of eventration as follows:

Cases in which diagnosis is regarded as proved: Left, 18; right, 4. Cases in which diagnosis was not proved, but regarded as reasonably certain: Left, 41; right, 2. Total left side, 59; total right side, 6. This makes a total of 65.

Since that time there have been reported many additional cases (Funk and Manges, Hurst, Steenhuis, Schaap, Louste, Fatou, Clopton, Stowell, Jewett, Beck, Jaffin and Honeij, Morrison, Muggia, Allan, Withington and Walton).

There are many other cases reported where the terms hernia and eventration were used together and where it was difficult to decide whether the cases reported were those of eventration according to the present conception of the term.

Pathological Anatomy. The pathology of the diaphragm has been studied at autopsy and at operation. In all of the cases of eventration it has been found that the walls of the diaphragm were thin, for example in 1784 Pyl reported a thin membranous sac. This was similar to the findings of Petit, and Meckel, in 1819, made a similar observation. Thoma, in 1882, noted the presence of some fibrous tissue scattered through the diaphragm on the affected side. In Benda's case there was found a lipomatous pseudohypertrophy of the diaphragm, and Motzfeltz reported a case associated with atrophy and fatty changes of the diaphragm.

Hypoplasia of the lung and also malformation of the lung have been frequently found associated with eventration. Other associated lesions observed are as follows: Dextrocardia, dilatation of the colon (called Hirschsprung's disease), dilatation of the stomach

and malformation of the mesentery. Hernias, particularly, have been found. Recently an interesting case of familial hernia was reported by Schreiber. The patient's father suffered from diaphragmatic hernia. She, herself, following the birth of a child, was supposed to have developed an eventration. All of her four children had some form of hernia.

It may be well to call attention to the observations concerning the outward appearance of the chest in cases of eventration of the diaphragm. It has been observed that there was no disturbance in the symmetry of both sides of the chest, even in those cases where malformation and hypoplasia of the lung was observed. This is apparently in accordance with the observations made by Ellis in 1917. He reported an interesting case of a young man, aged twenty years, in whom at autopsy there was found a complete absence of the left lung. There was no change in the outward contour of the chest. He found there were reported in the literature 18 cases, and while most of the cases were in infancy, or had been found in the fetuses, still the condition was not incompatible with adult life. One case at twenty years of age was reported, 2 cases at twenty-four years and 1 elderly patient at sixty-five years of age.

In this condition the opposite lung hypertrophies, and the other side is usually filled with fluid. This finding of symmetry of the chest, associated with absence, or malformation of the lung, is considered to be in favor of congenital origin of eventration, since no change in the contour of a chest has been observed in cases of eventration of the diaphragm.

Other criteria advanced by Thoma in favor of the congenital origin are:

1. The relative frequency of the involvement of the left side of the diaphragm. Attention is called to the embryonic development of the diaphragm. The right side in its development is protected by the liver, whereas the left side is in contact with many organs and is the last to close, and therefore there is the possibility of improper development there.
2. The frequent finding of eventration in the fetus and the newborn.
3. The association of other congenital anomalies.
4. The absence of symptoms over a long period of time.

Thoma felt that the faulty development of the lung allowed the diaphragm and the abdominal viscera to ascend in the thorax.

Doering claimed the condition was primarily a deficiency in the musculature of the diaphragm. Hoffman considered the condition an acquired one and suggested the hypothesis that the chronic dilatation of the stomach, by continued pressure upon the diaphragm, disturbed the blood supply of the diaphragm so as to favor the relaxation of it. This, however, has not been generally accepted.

Traction upon the upper surface of the diaphragm by adhesions has been advanced as a possible cause, but if this were so one should find retraction and diminished size of the chest.

Disease of the nerve has been considered to be responsible for the acquired type. Instances of high diaphragm associated with peripheral neuritis from diphtheria and other toxic states have been seen. A high diaphragm has been observed in poliomyelitis, also with progressive muscular atrophy, but it is clearly evident in these cases that the history will enable one to appreciate the cause.

Morrison, of England, recently reported 9 cases wherein the nerve was found to be secondarily involved with some disease within the chest, and in which a high diaphragm was found by means of the roentgen-ray. The right phrenic nerve was involved in 2 cases, and the left one in 7 cases. Three cases were secondary to carcinoma, 3 secondary to pulmonary tuberculosis, 1 associated with aneurysm and a new growth was found within the chest in the other 2 cases. It is interesting to note in an analysis of these cases that the age of the patient varies from forty-five to fifty-nine years. Autopsy on 2 of the cases revealed the phrenic nerve involved, in both cases with some degeneration of the muscle fibers of the diaphragm, although not to the extent that one would expect, and therefore Morrison suggests the possibility of an axillary innervation of the diaphragm.

Injury during birth has been considered as a possible cause of a high diaphragm. Weigert recently reported a case where trauma occurred during delivery. It was found by roentgen-ray that the diaphragm was high in the chest on the affected side, and after two months it occupied a normal position. Kofferoth made a similar observation relative to the diaphragm and observed paradoxical breathing in a case where forceps were used in delivery.

Therefore the weight of evidence at the present time is such as to favor:

1. Congenital origin.
2. Possibility of primary muscular defect.
3. Possibility of a nerve injury during birth.

Symptomatology. In certain cases of eventration of the diaphragm which were found at autopsy there were no symptoms associated with the condition during life. In other cases the symptoms found may be divided into two groups:

1. Thoracic group.
2. Abdominal group.

With reference to the thoracic group, the chief subjective symptom was dyspnea. In some cases it was present from childhood. Associated with dyspnea in some cases there were recurrent attacks of asthma associated with wheezing, occurring especially after meals. In Petit's case asthma was the chief complaint. Severe

cough has been a prominent symptom, with the expectoration of large quantities of sputa suggestive of bronchiectasis. In other cases severe pain in the chest simulating pleurisy is a prominent symptom. Associated with the pleurisy at times there has been the suggestion of effusion within the pleural cavity, so that a paracentesis was attempted with negative results. Sailer and Rhein reported such an experience. Cyanosis of a severe degree has been observed, and it was especially pronounced in the case of a child while in the prone position and disappeared when in the erect position. Exhaustion and fatigue are associated symptoms.

With the abdominal group, the chief complaint was referable to the gastrointestinal tract with some form of indigestion. The most prominent complaint was the feeling of pressure in the epigastrium and lower chest, associated with marked belching of gas. In other instances severe pain in the abdomen has been the chief complaint. At times the pain has been very acute and so severe as to suggest an acute appendix or an acute obstruction. This may possibly be due to the kinking of the gut, because of its peculiar relationship to the chest. Such an experience has been encountered with a dilated colon, that is, Hirschsprung's disease, associased with eventration of the diaphragm. It is not surprising that obstructive symptoms occur when one takes into account the peculiar appearance of the stomach and its relation to the chest, as has been demonstrated by means of the roentgen-ray.

There is a form of stomach observed in this condition called the spill and cup stomach, best seen in the oblique position in which the pyloric end of the stomach occupies a higher position within the chest than the cardiac end. It can be readily appreciated that if such a condition existed there would be a change in the anatomical relationship of the duodenum and the mesentery.

The possibility of eventration of the diaphragm as a cause of pain in the abdomen in children, due to some disturbance of the anatomical structure of the intestine, should be kept in mind. The pain in certain cases has been severe enough to suggest cholelithiasis.

In addition to the symptoms referable to the chest or abdomen, there is another group of symptoms related to the disturbance of the central nervous system in which there is present melancholia, inability to concentrate, tendency to mental fatigue and evidence of increased nervous excitability which might indicate a possible inferior development of the central nervous system.

Diagnosis. The following procedures have been used in the diagnosis of eventration of the diaphragm:

1. Schlippe's method of measuring the intragastric pressure during the different phases of respiration. It was by the use of this method that Hildebrand and Hess correctly diagnosed a case. However, it is well to call attention to the fact that there are

many conditions which influence the pressure. Minkowski reported positive findings in intragastric pressure when the breathing was of the costal type and in other instances when the breathing was of the abdominal type. The method is a complicated one, and for this reason, as well as the conflicting opinions given as to its value, is impractical.

2. The electrical excitation of the phrenic nerve. Efforts have been made to stimulate the phrenic nerve by means of an electric current and to note the effect of such stimulation upon the diaphragm as seen by the fluoroscope. This method has a distinct disadvantage in that it is difficult to excite in the living individual the phrenic nerve without influencing other viscera.

3. The use of the fluoroscope, and the use of the barium meal. In the majority of cases it is by this procedure that the diagnosis has been made. Certain criteria, when seen by means of the fluoroscope, have been considered diagnostic of eventration of the diaphragm. These are related to the observation of the movement of the diaphragm during respiration. It was found that the affected diaphragm moved on inspiration upward instead of downward. This has been called paradoxical breathing. This is not a constant finding, for it has been shown in certain proved cases of eventration that this did not occur, while in cases of hernia it was observed.

It would seem that the presence or absence of adhesions might influence this observation together with the movement of the contents of the mediastinum. In cases of eventration of the diaphragm, as studied by means of the fluoroscope, one can see an arched smooth line occupying a higher level in the chest than normal. This has been considered diagnostic of eventration in contradistinction to an irregular shadow as is observed in hernia.

Another observation, which has been considered of value, is the presence of a high fluid level in the stomach occupying an abnormal position within the chest. Through the evidence obtained by means of the barium meal, the relationship to the chest of the stomach, intestine and colon has been observed.

Roentgenographs of the patient taken in different positions will all show the relationship of posture and its influence on the contents of the stomach.

The roentgenographical examination is very important; in fact, the majority of cases have been diagnosed by this means. When a case is discovered by this method it frequently becomes a curiosity. The experience of the celebrated Schneider case in Europe is of interest in this respect. He visited many clinics. Each clinic subjected him to intensive ray studies, with the final result that he suffered from a severe burn.

4. The use of pneumoperitoneum. This procedure has been used to establish the diagnosis of eventration, but the danger associated with it makes it impractical.

FIG. 1.—Lateral view.

FIG. 2.—Position of barium-filled stomach in chest.

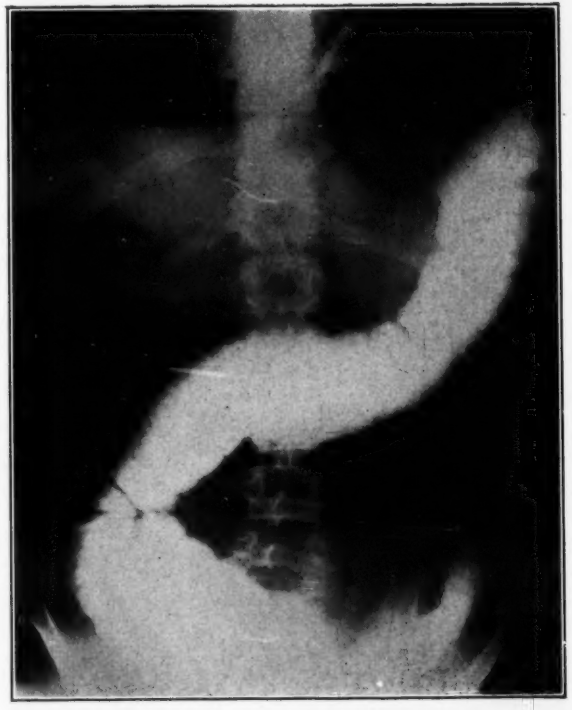

FIG. 3.—Position of barium-filled colon in chest.

FIG. 4.—Position of diaphragm in forced inspiration.

FIG. 5.—Position of diaphragm in forced expiration.

5. Diagnosis of eventration by means of physical signs. The physical signs of eventration are not entirely characteristic, but nevertheless are extremely valuable. The late Dr. Theodore Janeway made a correct diagnosis of eventration of the right diaphragm from physical examination. By percussion, tympany is usually found at one examination, and later this may be replaced by dulness. This change in the percussion findings is important. The breath sounds are found to be diminished, and at times there is heard splashing and metallic tinkle. These signs vary from day to day, dependent upon the contents of the stomach. The variability of the signs at different examinations should be carefully considered. They may be interpreted as evidence of pneumohydrothorax. However, in this condition the history will enable one to differentiate it from eventration, as well as the correlation of these signs and the study of the movements of the costal margin and the change in the subcostal angle.

Hoover has shown by experimental and clinical evidence the importance of careful study of the movements of the costal margins in the differential diagnosis of certain conditions above and below the diaphragm. The use of this method of examination is invaluable. It has proven a most helpful aid to me. Its value is not fully appreciated. This may be due in part to a lack of understanding or misconception as to the physiology of the diaphragm. The value and importance of any method of physical examination depends upon an understanding of the underlying physiology and clinical pathology. Accuracy in technical observation is only obtained by careful and repeated use of the method. Many physicians associate the function of the diaphragm with expansion of the chest and its effect on the vertical diameter of the chest. They are not familiar with the more important function of the diaphragm in its relation to the movements of the costal margin and its effect upon the subcostal angle. This is determined by the plane of activation of the muscle fibers of the diaphragm, the more horizontal the fibers, the greater the degree of activation.

The terms expansion and activation are used by many interchangeably. Failure to appreciate the relationship of the plane of activation of the diaphragm and the action of the intercostal muscles to the movements of the upper and lower costal margins is a common fault. In health this relationship is such as to give to the intercostal muscles the advantage and, therefore, the role of the diaphragm is not fully appreciated, whereas in certain diseased conditions the relationship is so changed as to make evident the role of the diaphragm. In some conditions the plane of activation of the diaphragm is more horizontal and therefore its action increased, whereas in other conditions there is an increase in the curve of the diaphragm, consequently its plane of activation decreased. This observation has been repeatedly proven both

clinically and experimentally. Attention to it will lead to more accurate interpretation of conditions affecting the lower chest and upper abdomen.

When one considers the position of the diaphragm in eventration and its effect on the horizontal plane, and also the position of the diaphragm in hernia, one can use this method of examination as a differential aid.

Funk pointed out its importance in a case which was discovered by the roentgen-ray. He then studied the movements of the costal margins, and stated that the condition could have been recognized if careful attention had been given to these movements. In a more recent communication Korns subscribes to this statement and reports a case to prove the same. In the case reported herewith this observation was extremely valuable and helpful. The importance of this means of examination in the recognition of eventration cannot be overestimated, since most cases are discovered by means of the roentgen-ray. Only a small percentage of patients examined are subjected to roentgenographical examination, and if, therefore, we have a clinical means of examination which will enable us to appreciate this condition I am sure there will be found a greater number of cases than are found at the present time.

Summary. 1. A case of eventration of the diaphragm is reported.

2. The literature as to the various theories of its causation, pathological anatomy, symptomatology and diagnosis is reviewed.

3. Special attention is directed to the possibility of the recognition of this condition by clinical means instead of, as is now done, by means of the roentgen-ray.

4. An important aid is the careful study of the movements of the costal margins, as first described by Hoover.

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EXPERIMENTAL STUDIES ON THE ENTRANCE OF BILE INTO THE DUODENUM.

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In a previous communication,[1] an experimental study of the pressures existing in the various parts of the biliary outflow system was presented. These experiments indicate that the pressure in the common duct is relatively low (60 to 70 mm. of bile) and varies little; that normally the sphincter of Oddi offers to pressure exerted from the common duct side, a resistance of 120 to 130 mm. of saline; that the substances usually present in gastric chyme, when placed on the papilla of Vater, lessen the tonus of the sphincter somewhat, in our experiments one-fifth to one-sixth of the original figure; that 25 per cent magnesium sulphate placed on the papilla acts likewise; that atropin and adrenalin, administered subcutaneously, also reduce the tonus of the sphincter while pilocarpin increases it; that the slight variations in the pressure within the gall bladder are due to tonus changes, the musculature of its wall possessing little, if any, actual contractile power; that reciprocal or contrary innervation or action between sphincter and gall bladder is not demonstrable by the usual methods employed to demonstrate it; and that the intra-abdominal pressure at the end of an inspiration effects a comparatively tremendous increase in the intravesical pressure and almost none in the intraductal pressure.

If these experimental data are applicable in the explanation of normal physiological processes, then, apparently, the variations in the tonus of the sphincter of Oddi and the changes in the intra-abdominal pressure are the two factors of greatest importance in controlling the entrance of bile from the gall bladder and liver into the duodenum. It seems as if the contractile power of the gall bladder wall is of little significance in the emptying act. While these conclusions seem justifiable in view of our studies on the possible pressure variations, they have been supported by observations of what actually takes place both in the operated animals and those fully recovered from operative procedures. These observations will be recorded here.

Spontaneous Activities. (*a*) *Gall bladder.* A spontaneous gross contraction of the gall bladder with the peritoneal cavity open, was never seen throughout our experiments. It may be added, furthermore, that roentgenological studies on intact animals by means of small silver buttons sewed on the gall bladder,[2] and by means of roentgen-opaque solutions injected into the gall bladder,[3] have proved negative in regard to visible spontaneous contractions.

(*b*) *Bile flow.* There seems to be a continuous, although varying rate of bile flow into the hepatic ducts. Bile, however, may not enter the duodenum in the fasting, anesthetized animal for periods varying from fifteen minutes to three-quarters of an hour. When it did enter, two types of flow were observed: (1) Slow, irregular, intermittent oozes of a few drops, and (2) somewhat larger, regular, intermittent escapes synchronous with each inspiration.

Stimulation of the Gall Bladder Locally. *Electrical.* A faradic current of varying intensity was used.

EXPERIMENT 1. Dog 3559, male, weighing 8 kilos. Ether anesthesia and median laparotomy. Two cubic centimeters of 0.5 per cent methylene blue solution were injected into the gall bladder. A thin rubber tube was then passed through a small opening on the greater curvature of the stomach into the duodenum. The duodenal content was thus observed for one-half hour. Only light brown bile unstained by the dye was seen. Various points on the surface of the gall bladder, along the cystic duct, and the tissues surrounding the common duct were submitted to faradic stimulation. Neither a perceptible contraction nor a change in size occurred. Dyed bile did not enter the duodenum.

EXPERIMENT 2. Dog 3581, male, weighing 7½ kilos. Ether anesthesia and median laparotomy. The duodenum was incised and a small glass cannula (2 mm. in diameter and 2 cm. long) was inserted through the sphincter of Oddi and tied securely into the common duct at the papilla. The duodenal and abdominal wounds were then closed. The following day laparotomy under ether anesthesia was again performed. The gall bladder, which was found collapsed, was refilled with 12 cc of dog bile and the

faradic current applied as in the previous experiment. A contraction did not result. The cystic duct was ligated and a straight glass manometer was tied into the fundus of the gall bladder. The subsequent application of the faradic current did not produce a rise in the pressure within the gall bladder.

Artificial Distension. Varying degrees of distension of the organ with air and fluid were instituted and the effect on its contractile activities noted.

EXPERIMENT 3. Dog 3257.[1] In this dog, while studying the pressures in the entire duct system, from a few cubic centimeters up to 35 cc of saline were injected into the gall bladder without causing a perceptible contraction.

EXPERIMENT 4. Dog 3394, female, weighing 8 kilos. A collapsed rubber balloon was inserted into the emptied gall bladder and connected with a water manometer. Inflation of the balloon with pressures from 20 to 100 mm. of water did not cause a contraction.

Operative Manipulations. Handling, squeezing, or pinching the organ, grasping with an artery clamp, piercing with a needle, or cutting the wall, did not cause a generalized contraction. Occasionally, a slight, shallow, linear spasm adjoining the traumatized area was seen.

Manual Expression. The emptying of the contents of the gall-bladder into the duodenum by manual expression ordinarily requires considerable force. The slightest pressure, however, is sufficient to accomplish this when a duct is cut into or across at any point between the sphincter and the neck of the gall bladder, or when the sphincter is kept patent by a glass cannula as in Experiment 2.

EXPERIMENT 5. Dog 3432, male, weighing 12 kilos. Ether anesthesia and median laparotomy. Methylene blue solution was injected into the gall bladder and the duodenum opened opposite the papilla. Atropin, gr. $\frac{1}{100}$, was administered subcutaneously to relax the sphincter.[1] The abdominal wound was then temporarily closed and antero-posterior pressure applied vigorously for ten minutes. On reopening the abdomen, no dyed bile was found in the duodenum. The abdomen was again closed and the lower thorax and upper abdomen squeezed laterally. The duodenum now contained most of the dyed content of the gall bladder. The common duct was cut across above the sphincter and the slightest pressure on the gall bladder sufficed to expel dyed bile into the free peritoneal cavity.

The Respiratory Squeeze. In the roentgenological studies, already mentioned, of Abramson[3] and Winkelstein,[2] which were made on animals recovered from operative procedures and in good health, a definite craniocaudal squeeze of the gall bladder with each inspiration could be seen. Furthermore, we have also described how this respiratory squeeze effects a large fluctuation in the intravesical

pressure.[1] It is apparent, however, that this increase of pressure may be ineffectual in the emptying process if the sphincter of Oddi remains closed with a sufficient tonus resistance to block the entrance of bile into the duodenum. There is the further possibility that the intra-abdominal pressure may cause a simultaneous pressure increase in the duodenum quantitatively like that in the gall bladder and so prove ineffectual even with the sphincter open. That this is not the case was demonstrated by the following experiment in which the pressure in the duodenum, empty or distended, rose merely 5 to 15 mm. with the respiratory change. Pressure within the gall bladder, it will be recalled, rose to 100 mm. at the end of inspiration.[1]

EXPERIMENT 6. Dog 3926, male, weighing 8 kilos. Ether anesthesia and median laparotomy. A straight glass tube was tied into the duodenum at the level of the papilla and connected to an upright water manometer. The abdominal wound was closed tightly about the glass tube and the respiratory fluctuations noted.

	Inspiration.	Expiration.
Duodenal contents	5 to 10 mm.	0
10 cc saline in duodenum . . .	10 mm.	0
20 cc saline in duodenum . . .	10 to 15 mm.	0

The following experiment was next devised to study the effect of respiration when the sphincter is open or relaxed. The results seem so striking as to make this experiment possibly of prime importance in the problem at hand.

EXPERIMENT 7. Same dog as in Experiment 2. After the small glass cannula had been fixed in the common duct partly through the papilla so as to keep the sphincter open, and methylene blue injected into the gall bladder, the duodenal contents were observed with the duodenum and abdominal cavity still open. With each inspiration dyed bile entered the duodenum from the gall bladder. In twenty minutes, the normally distended gall bladder was rendered flaccid. The duodenal and abdominal wounds were then closed and the animal allowed to recover. Eighteen hours later, laparotomy was again performed. The gall bladder was found collapsed and practically empty containing a fraction of 1 cc of dyed bile. The jejunum and ileum contained stained bile.

This experiment shows that the respiratory act squeezes bile out of the gall bladder into the duodenum when the sphincter is open and demonstrates the importance of the sphincter in the normal filling of the gall bladder.

Electrical and Drug Stimulation of the Nerves Innervating the Gall Bladder. *Electrical.* The following experiment is typical of several attempts made to cause a contraction or relaxation of the gall bladder or an expulsion of its contents by means of faradic stimulation. These attempts were invariably attended by negative results.

EXPERIMENT 8. Dog 3359, male, weighing 8 kilos. Ether anesthesia and median laparotomy. One end of a thin, soft, rubber tube was inserted into the duodenum through an opening in the greater curvature of the stomach and the other end led out through a stab wound in the lateral abdominal wall. The abdominal wound was then sewed up tightly. The vagus nerve was exposed in the neck and the animal allowed to come out of the anesthesia. The faradic current was then applied to the uncut nerve and later to its cut end. Dyed bile did not appear in the duodenum. The abdominal cavity was again opened and the electrodes applied to the tissues about the cystic and common ducts and along the lesser curvature of the stomach. Neither a contraction of the gall bladder nor a change in its size was seen and dyed bile did not enter the duodenum.

Drug Stimulation. In the previous experiments on the pressure factors in the biliary duct system,[1] pilocarpin, adrenalin, and atropin, were administered repeatedly in order to affect the involuntary nerves supplying the sphincter of Oddi and the gall bladder. While these drugs caused some pressure changes within the gall bladder these were only in the nature of tonus variations. Actual gross contractions, changes in the size of the organ, or expulsion of its contents were not seen. In the following experiment, performed later, a decrease in the size of the gall bladder occurred after pilocarpin. This had no practical effect since no emptying took place, although the dosage used was very large.

EXPERIMENT 9. Dog 3432, male, weighing 12 kilos. Ether anesthesia and median laparotomy. A thin, rubber tube was inserted into the duodenum through an opening in the greater curvature of the stomach and methylene blue was injected into the gall-bladder. Pilocarpin, $\frac{1}{12}$ gr., was injected intravenously. The stomach and intestines were thrown at once into a severe tonic contraction. The gall-bladder wall tightened generally and the organ decreased one-third in size. Dyed bile, however, did not enter the duodenum (simultaneous contraction of the sphincter of Oddi?). Atropin, $\frac{1}{75}$ gr., was given subcutaneously, and the contractions disappeared at once but dyed bile did not enter the duodenum.

Secretin. In three dogs, an extract of the duodenal mucosa was made in the usual manner and 2 cc were injected intravenously. There was no apparent effect on the motor activities of the gall bladder.

Reflex Stimulation of the Gall Bladder. In the studies on the pressure factors[1] many chemicals were instilled in the opened or closed duodenum over the papilla of Vater. Some of these, notably magnesium sulphate and peptone, relaxed the sphincter of Oddi. None, however, caused a visible contraction or emptying of the gall bladder. Distending or irritating the mucosa of the stomach

and duodenum, stretching the pylorus, pinching and rubbing the mucosa of the duodenum, were likewise without appreciable effect.

It must be borne in mind, however, that these observations were made with the animal under ether anesthesia, the abdominal cavity open, and often with the duodenum and stomach incised. In the belief that the factors of trauma and anesthesia interfere with the normal physiological nerve responses, a different type of experimentation was next employed. These experiments have already been briefly reported,[4] but will be described here in full.

In general, the experimental procedure consisted in anesthetizing the dog, injecting a dye stuff into the gall bladder, inserting a soft rubber tube into the duodenum through an opening in the greater curvature of the stomach, leading this tube out through a stab wound in the lateral abdominal wall, suturing the laparotomy wound, and allowing the animal to recover. Following the recovery from the anesthesia and the operation, observations on the duodenal contents were made, chiefly on the effect of the injection of warm saline and magnesium sulphate into the duodenum. It was found that the dyestuff could be more readily distinguished in the supernatant fluid when the bile pigments were precipitated by saturated lead acetate or barium sulphate

EXPERIMENT 10. Dog 3665, male, weighing 14 kilos. Ether anesthesia and median laparotomy. Two cc of 0.5 per cent methylene blue were injected into the gall bladder. A thin, soft, rubber tube was passed through an opening in the anterior stomach wall at a point near the greater curvature, into the duodenum. The stomach end of the tube was led out through a stab wound in the lateral abdominal wall. With the abdomen open, 40 cc of 25 per cent magnesium sulphate were repeatedly injected into the duodenum and aspirated. Only light brown bile unstained by the dye was obtained. The laparotomy wound was then closed and the animal allowed to recover.

Observations. Nineteen hours postoperative; before and after the instillation of warm saline and magnesium sulphate into the duodenum, only yellow bile was obtained.

Twenty-four hours postoperative; thirty-five minutes after bread and water was eaten by the dog, 3 cc of dark green dyed bile were aspirated.

Forty-six hours postoperative; before and after warm saline, pale greenish-yellow bile was aspirated. After 40 cc of 25 per cent magnesium sulphate, however, bile, stained deeply green, was recovered.

Forty-nine hours postoperative; after saline, magnesium sulphate, and food, only light yellow-brown bile was found in the duodenum.

Subsequent Observations. During the next four days, the effect of saline, magnesium sulphate, peptone, and food, was observed. Only bile varying from yellow to brown without dye was seen. On

the seventh postoperative day, the abdomen was opened under anesthesia. The gall bladder was normally distended with 10 cc of brown bile. The tonus of the sphincter of Oddi was preserved; it was found to measure 115 mm. of saline (average tonus).

Discussion. Apparently, after magnesium sulphate and food and not after warm saline, bile from the gall bladder entered the duodenum. It seems probable also that the dyed specimen of bile left the gall-bladder in forty-six to forty-nine hours.

EXPERIMENT 11. Dog 3740, male, weighing 7 kilos. The procedure was the same as that in the previous experiment.

Observations. Fifteen minute postoperative; 2 cc of brown bile were aspirated from the duodenum.

Twenty-two hours postoperative; before and after warm saline, only yellow-brown bile was recovered. Following the instillation of magnesium sulphate, bile, moderately green-stained, was aspirated.

Forty-six hours and the next three days postoperative; after saline, magnesium sulphate, and food, yellow-brown bile was found in the duodenum.

Subsequent Observations. Under anesthesia, the dog's abdomen was opened six days after the operation. The gall bladder was found normally distended with 10 cc of moderately dark brown bile.

Discussion. After magnesium sulphate and not after saline, bile from the gall bladder entered the duodenum. The gall bladder was probably emptied of the dyed bile in twenty-two to forty-six hours.

EXPERIMENT 12. Dog 3760, male, weighing 14 kilos. Procedure as in the previous experiment. 100 mg. of phenoltetrachlorphthalein was also injected into the gall bladder.

Observations. Fifteen minutes postoperatively; 3 cc of brown bile without dye were aspirated.

Twenty-one hours postoperatively; before and after saline unstained bile was found in the duodenum. After magnesium sulphate, green-dyed bile containing phenoltetrachlorphthalein was aspirated.

Twenty-five hours postoperative; one-half hour after food, only brown bile without dye was recovered.

Subsequent Observations. For six days, after saline, magnesium sulphate, and food, yellow to brown bile was obtained. On the seventh day, 50 mg. of indigo carmine was injected intramuscularly. Twenty-four hours later, after magnesium sulphate and not after saline, dyed bile appeared in the duodenum. Under anesthesia, the abdomen was then opened and the gall bladder was found to contain 7 cc of bile stained a deep green by the dye.

Discussion. It does not seem necessary to make any other comment than to state that the gall bladder was probably emptied of the dyed bile in twenty-one to twenty-five hours.

EXPERIMENT 13. Dog 3916, male, weighing 8 kilos. The procedure was the same as in the previous experiment except that 5 cc of Neo silvol, stained by indigo carmine, was injected into the gall bladder after the withdrawal of 5 cc of bile.

Observations. In brief, it was found that after magnesium sulphate and not after saline, dyed bile entered the duodenum and that the dyed bile had left the gall bladder in forty-eight hours.

Summary. A full discussion of these experiments and their possible significance will be reserved for a future publication. The experimental observations may, however, be summarized briefly here.

1. No evidence was found of spontaneous contractions of the gall bladder in the dog, either under anesthesia or when fully recovered.

2. It is possible to empty the gall bladder by manual expression after the sphincter of Oddi is relaxed, with the peritoneal cavity open or closed.

3. The respiratory squeeze, that is, the increase in intra-abdominal pressure at the end of inspiration, also effects an expulsion of bile into the duodenum from the gall bladder when the sphincter of Oddi is relaxed.

4. Direct or reflex stimulation of the gall bladder, whether it be by faradization, drugs, hormones, chemicals, or mechanical means, does not cause a contraction of the gall bladder, or an appreciable change in size, or any emptying, in the experimental animal under anesthesia.

5. In an animal, however, which has fully recovered from the operative procedures, following the instillation of 25 per cent magnesium sulphate or the passage of gastric chyme into the duodenum, and not after normal saline, there is an entrance of bile from the gall bladder into the duodenum.

Whether the more normal physiological conditions in the last instance permit of gall bladder contractions sufficiently strong to expel bile seems extremely doubtful from our experimental observations. It is more probable that certain agents, viz., magnesium sulphate and gastric chyme, relax the sphincter of Oddi and that then, the intra-abdominal pressure at the end of each inspiration expresses some bile from the gall bladder into the duodenum.

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A NEW METHOD FOR STUDYING PURE GASTRIC SECRETION.*

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We have been accustomed, clinically, to study gastric secretion by means of the various types of test meals. In this way, however, we are dealing with gastric contents which contain not only the gastric juice, but also constituents of the test meal, besides swallowed saliva.

The first accurate observations on pure gastric juice in man were made by Dr. Beaumont in 1833, on a Canadian voyageur who, by the premature discharge of his gun, was left with a permanent gastric fistula. By this method, samples of gastric juice could be secured, but not while the digestive process was actually in progress. To make the collection of such a sample possible, experiments in animals were resorted to. Heidenhain isolated portions of the stomach wall as pouches opening through fistulæ on the abdominal wall. The objection to this procedure was that the secretion in the isolated pouch did not necessarily correspond to that occurring in the main stomach, since the connection of the pouches with the central nervous system was severed. In order to overcome this disadvantage, Pavlow[1] devised the ingenious operation of a miniature stomach which remained connected with the main stomach without severing the nerve connections. Naturally, this procedure is applicable only for experimental purposes in animals. In man, it is only the gastric fistula cases with stenosis of the esophagus, similar to Dr. Beaumont's patient, which offer the pure type of gastric secretion; but such patients are rare, and gastric problems can only be definitely answered by studies upon many subjects[2]. There is no organ in the body, the function of which is more influenced by individual reaction, than the stomach. Gastric juice without food admixture has usually been collected by aspiration of the fasting stomach, but contents thus obtained suffer the disadvantages of having been in the stomach for varying lengths of time, of not being produced during the cycle of digestion, and of being contaminated by swallowed saliva or regurgitated bile.

In the course of the author's studies on duodenal alimentation, the two-tube method[3, 4] was found very satisfactory for obtaining pure gastric secretion during the act of digestion. The technic is comparatively simple. The patient swallows the duodenal tube (Einhorn type), which is allowed to pass into the duodenum in the usual way. After it is proven definitely in place, another duo-

* (From the Laboratory and Medical Division of the Lenox Hill Hospital, Service of Dr. J. Kaufmann.)

denal tube is then swallowed, but this second one remains in the stomach. When gastric juice is wanted, duodenal alimentation should be started through the duodenal tube, best done by means of the regular Einhorn Duodenal Feeding Outfit. The author has found that in response to the duodenal feeding there is an immediate secretion of gastric juice which can be easily aspirated from the stomach, through the gastric tube.

It is wise to empty the stomach of any contents that it may contain before the duodenal alimentation is started. Then too, one must be certain that the tube in the stomach rests in its most dependent portion, otherwise aspiration will not bring forth all the gastric secretion. At times, it may require the roentgen-ray to see the proper position of the tube. It is often necessary to change the posture of the patient from reclining to sitting, or *vice versa*, or from one side to another.

The gastric secretion starts almost immediately after the injection of the first 20 to 30 cc of fluid into the duodenum, and is most marked during, or right after, the feeding (which should take twenty minutes), but often continues for about thirty minutes to an hour after the duodenal alimentation has been stopped.

We found several important factors which influenced the gastric secretion.

Type of Patient. It was shown[4] that the amount and character of gastric juice which can be collected in response to duodenal feeding depends upon the type of patient dealt with, and compares very closely to what the gastric secretion would be in that same patient in response to the gastric test meal. Thus, a patient with an achylia gastrica shows no gastric secretion in response to duodenal feeding. A patient with a mild irritative form of gastric disorder offers a moderate amount of gastric secretion—about 100 cc, while patients with a marked irritative form of gastric function, as cases of alimentary hypersecretion, give as much as 280 cc of pure gastric juice in response to a duodenal feeding.

Type of Duodenal Feeding. Most of the experiments were done with duodenal alimentation, consisting of a mixture of 7 ounces of milk, 2 eggs, ½ dram of lactose, 1 square of butter and a pinch of salt.

Different types of feeding were undertaken in the same person to note any possible difference in the response of gastric secretion. The most striking example was seen in a patient with a gastric ulcer and alimentary hypersecretion; comparative experiments, after individual feedings with 8 ounces of saline, 8 ounces of beef broth, 8 ounces of milk-egg mixture, and 8 ounces of thick strained oatmeal gruel, showed the least amounts of gastric secretion, that is, 100 cc and 138 cc following the saline and the broth respectively; the greatest amount (377 cc) was stimulated by the 8 ounces of gruel, while the milk-egg mixture gave 286 cc.

CHART.—GASTRIC SECRETION AFTER DUODENAL FEEDING WITH VARIOUS SUBSTANCES.

Time of aspiration after starting duodenal feeding.	Normal saline (8 oz.)			Beef broth (8 oz.)			Milk-egg mixture† (8 oz.)			Thick oatmeal gruel (8 oz.)		
	Quantity of aspirated gastric secretion.	Free* HCl.	Total* acid.	Quantity of aspirated gastric secretion.	Free HCl.	Total acid.	Quantity of aspirated gastric secretion.	Free HCl.	Total acid.	Quantity of aspirated gastric secretion.	Free HCl.	Total acid.
15 minutes	70 cc	22	38	90 cc	44	53	98 cc	51	69	175 cc	54	62
30 "	30 cc	36	44	30 cc	52	62	80 cc	51	64	110 cc	54	62
	Duodenum empty											
45 "	....	..	..	18 cc	52	60	50 cc	48	68	35 cc	52	62
				Duodenum empty								
60 "	....	..	..	....	..	..	38 cc	54	68	25 cc	54	66
							Duodenum empty					
75 "	....	..	..	....	..	..	15 cc	60	70	25 cc	74	78
										Duodenum empty		
90 "	....	..	..	....	..	..	5 cc	4	20	7 cc	32	20

* As determined by titration with tenth-normal NaOH per 100 cc.

† Consists of 7 ounces of milk, 2 eggs, ½ dram of lactose, 1 square of butter, pinch of salt.

From repeated experiments with similar results, this difference was explained by the finding that the longer the feeding remained in the duodenum, as evidenced by aspiration, the longer did the gastric secretion continue. In all the tests, as soon as the duodenum became empty, the gastric secretion practically ceased. The saline and broth passed out of the duodenum most quickly, while the gruel stayed longer than the milk-egg mixture.

Discussion. The excitation of gastric secretion by application of food substances to the duodenal mucosa, had not heretofore been demonstrated sufficiently conclusively in man.

In animals, this was first shown by Pavlow and his coworkers.[1] Gross[6] employed a duodenal and a gastric fistula in animals, and observed that when meat extract was put into the intestines, a stimulation of the gastric glands resulted. Similar animal experiments with different food agents are reported by Zeliony,[7] Lonnquist,[8] Chittenden, Mendel and Jackson,[9] Edkins and Tweedy,[10] and Tomaszewski.[11]

The most recent and very detailed studies along these lines were published by Ivy and McIlvain.[12] Their experiments were made on dogs, with a Pavlow pouch in the stomach, and a Thiry's fistula in the duodenum and jejunum. In this way, there was produced a loop of duodenum and jejunum fifteen to eighteen inches long, to which substances could be continuously applied, and the resulting secretion in the Pavlow pouch noted. A great number of active and constant excitants were demonstrated. These workers also made experiments upon two men in whom twentieth-normal HCl was injected into the duodenum through a duodenal tube, after which gastric secretion resulted.

Regarding the mechanism concerned in the excitation of gastric secretion by way of the upper intestines, several factors may play a role. While it seemed certain to the writer that secretion continued as long as food substances remained in the duodenum, this was not due to a simple distention of the duodenal loop. Ivy and McIlvain[12] found that when the loop was distended with from 50 to 75 cc of air or water, no stimulation of gastric secretion occurred. Pavlow suggested that it may be due to a local secretory reflex from the intestinal mucosa to the gastric mucosa. On the other hand, it may be a long reflex to the cerebral centers, and a centrifugal response with either a secretory or vasomotor effect. The possible stimulation by secretin produced in the intestinal mucosa must also be considered, although the almost immediate appearance of the gastric secretion after the duodenal feeding, as is regularly noticed in the human being, without a latent period, speaks somewhat against the hormone element. The possibility of a psychic factor in influencing the results is, of course, always to be kept in mind. Definite explanation must therefore be withheld.

Summary. 1. The two-tube system, with the physiological phenomenon that gastric secretion takes place in response to duodenal feeding, offers a new method whereby we can collect large quantities of pure gastric juice, as soon as it is secreted, during the act of digestion, and without admixture of any test meals.

2. The instigated gastric secretion differs with various articles of food, and continues as long as the particular food contents remain in the duodenum.

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THE NEOPLASTIC NATURE OF THE LEUKEMIC PROCESS.

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The conception of the leukemic process as a truly neoplastic one is not new, and has been supported by a number of writers, *e.g.* Banti,[2] Babes,[1] Ribbert,[14] Benda,[3] Mallory[11] and others, but has not obtained wide acceptance. Sternberg has attempted to show that the large-celled form of lymphatic leukemia is a neoplastic process (leukosarcomatosis), but the other forms of leukemia are not explained on his hypothesis. An infiltrative mode of growth is insufficient evidence of the neoplastic nature of a disease, and this alone is sufficient to invalidate the conception of Banti. Lenaz[10] has attempted to form a definition of neoplasia, and comes to the conclusion that all forms of leukemia are neoplastic and carefully excludes all those hematological reactions of similar character which have no histological relationship with the leukemias. This is doubtless a proper distinction to make, but the very fact that "leukemoid" reactions do occur independently of leukemia would seem to indicate that a similar impetus of some kind is at work. If leukemia can properly be regarded as neoplastic it is essential that a definite tumor should be demonstrated, even if the blood picture itself and the infiltrations of the tissues cannot be regarded as being of metastatic nature.

It is not uncommon to regard all forms of leukemia as of hyperplastic nature, but the absence of a clear conception of the nature of such a process is a bar to its acceptance. If the term hyperplasia be confined to those processes in which an increase of normal cells in normal arrangement is the essential feature it will be obvious that leukemia is not of this nature. An inflammatory reaction differs essentially from a neoplastic one, in that many phases of cell activity and structure are present at the same time, while in a tumor only one type of cell proliferates in an atypical manner, that is, there are a number of phases in an inflammatory focus but only one in a neoplastic one. The application of these conceptions to the leukemic process should present little difficulty, so long as the changes in the hematopoietic organs and not the characters of of the blood picture be regarded as the essential features.

If the lymphatic type first be considered (lymphadenosis) in its chronic form, it is to be noticed that two types of blood picture may occur; the two types (shown below) may occur in the same case at different times, but when the first type has disappeared it never returns.

TABLE I.—TYPES OF DIFFERENTIAL COUNT IN CHRONIC LYMPHATIC LEUKEMIAS.

	Type I, Per cent.	Type II, Per cent.
Polymorphonuclears	22	7.9
Eosinophiles	2	0.15
Basophiles	0	0.2
Monocytes	4	1.85
Lymphocytes	72	87.4
Metamyelocytes	0	0.1
Myelocytes	0	0.25
Myeloblasts	0	1.8
Lymphoblasts	0	0.2
Plasma cells	0	0.15

It will be noted that the essential difference between the two types is the presence of immature cells of the myeloid series in the second type, in which also nucleated red cells are much more common.

Acute lymphadenoses usually are of the second type, and a case with no immature myeloid cells is a great rarity. Naegeli[12] regards the presence of such cells simply as a result of irritation, but does not state the nature of the stimulus. Fig. 1 shows the appearances of a section of bone marrow from a case of chronic lymphadenosis, which had reached the second stage. It will be seen that a mass of lymphocytes is surrounded by hyperplastic marrow tissue, which is only incompletely separated from the lymphocytic mass. Fig. 2 shows a section from the marrow of a case of carcinoma of the breast with metastases in the bones; here there is a mass of carcinoma cells surrounded by a zone of hyperplastic myeloid tissue

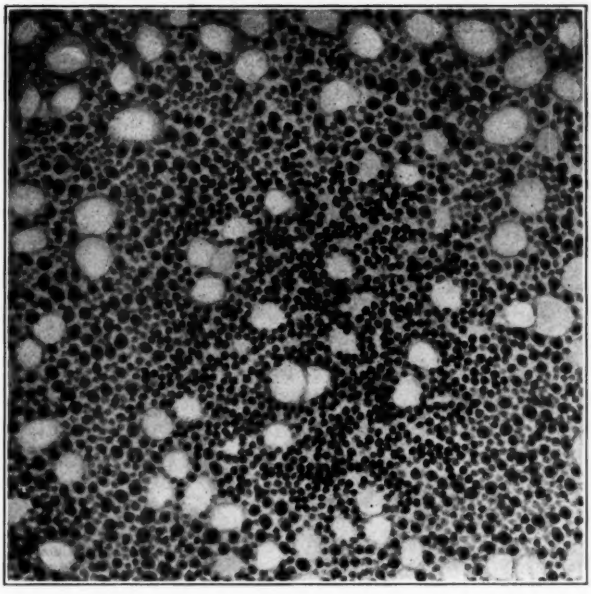

FIG. 1.—Section of marrow from cases of chronic lymphadenosis. The section shows a mass of small lymphocytes in the center and this is surrounded by myeloid tissue in a state of well-marked hyperplasia.

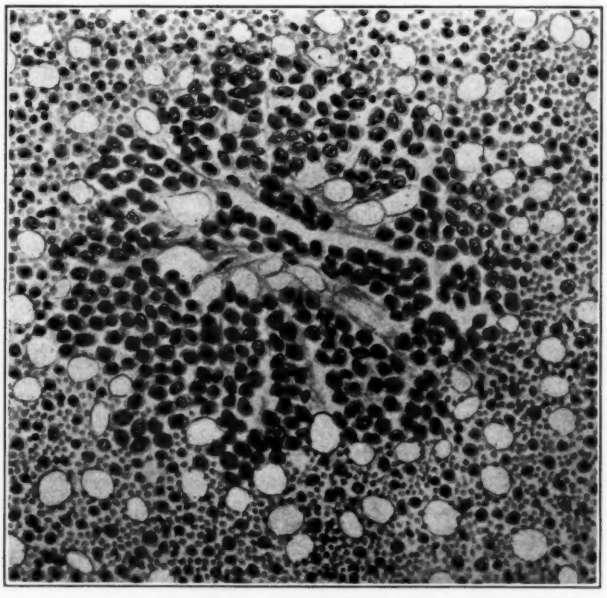

FIG. 2.—Section of marrow from case of metastatic carcinoma of bone. The central part of the field shows a mass of epithelial cells which are surrounded by intensely hyperplastic marrow tissue. The resemblance to Fig. 1 is very striking and the sole difference is found in the nature of the cells composing the central mass.

of a character identical with that seen in Fig. 1. The blood in this case showed 12.75 per cent of immature myeloid cells, that is, a percentage even higher than that found in the second type of lymphadenosis recorded above. The hematological distinction between the two conditions lies in the much greater total number of leukocytes and much higher percentage of lymphocytes in leukemia than in metastatic cancer of the marrow, but the myeloid picture does not differ appreciably in the two diseases. The fact that leukemic proliferations of marrow differ in their arrangement from normal marrow can be seen quite easily in sections and the leukemic process differs also from the ordinary hyperplasia associated with severe leukocytosis. In lymphadenosis these differences are naturally more marked than in myelosis, as here the former process causes growth of a foreign tissue in the marrow which displaces and destroys the myeloid tissue—this would appear to be a true neoplasm.

The blood picture is certainly more difficult to interpret than is the histological picture in the hematopoietic organs, as here there are two distinct features, namely, the emigration of immature leukocytes as the result of the simple hyperplasia of the marrow around the lymphocytic foci and the flooding of the circulation with lymphocytes from the tumor-like masses.

The first appearance of immature myeloid cells in the blood seems to correspond to the time when focal points of tenderness of bones can first be noted clinically, and such points of tenderness always correspond to microscopical areas of lymphocytic infiltration. It must be recalled also that Naegeli[12] has recorded a case of typical lymphatic leukemia in which spontaneous fracture of a rib occurred.

The tumor-like foci in cases of myelosis are usually composed only of myeloblasts, which form groups of 20 to 200 cells in which no signs of development into premyelocytes can be found, although the surrounding tissue shows this mode of maturation in great quantity, that is, these are monophasic foci. Rarely the foci in myelosis are composed of myelocytes and even less commonly of premyelocytes, and in these cases the blood picture at the end of life is predominatingly myelocytic or premyelocytic instead of myeloblastic, as is usually the case. These facts appear to show conclusively that cells from the monophasic foci can emigrate into the blood stream and, if this is so, and if they are tumor cells, it should be possible to recognize them in the blood before the end of the disease. If the cells in films from cases of myelosis be carefully examined it is always possible to find that the percentage of atypical myeloblasts (premyelocytes or myelocytes according to the type of case) increase as the disease progresses until, toward the end, few typical cells of the group can be found in the blood. It is equally important to note that such abnormal forms are not

found in the blood in cases of metastatic tumors of bones. It is inconceivable that the abnormality of some of the blood cells depends upon injury by an unknown agent, as the rate of reproduction is so much greater than normal—an occurrence which is extremely improbable in injured cells. The general appearance of the marrow is that of an intensely active organ, such as could scarcely be the result of toxic injury.

The length of the clinical history of many cases of leukemia can be employed as an objection to the neoplastic conception only if the disease be regarded as a malignant neoplasm, which would seem to be a necessary conclusion only in relation to the acute forms of the type which were excluded from the neoplastic hypothesis by Sternberg.

In brief, the conception put forward in this paper is that of a neoplastic process, which, like other tumors, is more rapid in its course when composed of immature cells and which gives rise to a striking blood picture by two means, namely, irritation of the bone marrow and emigration of the tumor cells themselves in progressively greater numbers as the disease progresses and the amount of functional marrow decreases.

The appearances of the marrow, and of the blood (Piney[13]) show that the emigration of immature cells cannot be attributed to a depletion of the tissue and consequent paucity in mature forms.

It is necessary to mention briefly some of the arguments in favor of the other views of the nature of the leukemic process. An infective origin of, at least, some forms of the disease has frequently been very strongly supported, for example, Sternberg[15] has contended that the acute myeloblastic form is not a special malady, but is a peculiar reaction to a variety of infections. He claims that it is possible to produce an intense myelocytosis in the blood and well-marked myeloid change in the tissues by injection of streptococci, but he appears to ignore the essential feature of leukemia, namely, the focal arrangement of masses in the marrow.

Von Hansemann[7] propounded a most attractive view, which can at present be little more than a working hypothesis: He suggests that the changes in the tissues in leukemia are so unlike true tumors that no other possibility than infection remains to be considered, and he suggests that leukemia may be a condition secondary to an infection. Herz[8, 9] has taken up a similar attitude, and pointed out that lymphomata in the liver are common in typhoid fever, and suggests that such tissue formations may be the morphological basis of a predisposition to leukemia. The experimental work of Ellermann[4, 5, 6] on the leukosis of fowls is the most striking evidence in favor of the infective theory, but the histological changes found in these animals differ from those found in human leukemia in that they appear to be purely hyperplastic and metaplastic.

The appearances of the neutrophile polymorphonuclear leukocytes and in fact of the neutrophile cells as a whole in leukemia is very striking, because there is a shift to the left of the Arneth index, that is, a decrease in nuclear complexity with even the appearance of quite immature forms, namely, myelocytes, but at the same time there is also an increase in the number of many-lobed polymorphonuclear leukocytes—some with as many as seven lobes in the nucleus. These are not the appearances found in infective diseases. The fact that eosinophile leukocytes may increase at the same time as the neutrophiles is some evidence against the conception of an infection because, as a rule, the eosinophiles fall when the neutrophiles increase in number.

The occurrence of such a condition as myeloblastic leukemia is very difficult to reconcile with an infective origin, as it is now known that the granular cells increase mainly by division of preëxisting granular cells (myelocytes) and not by derivation from the non-granular myeloblast (Ellermann[6]), which appears to fulfill its function in embryonic life. If this fact be admitted it is obvious that the excessive proliferation of myeloblasts cannot be explained by the presence of an additional demand for granular cells, as this should result in an increase of myelocytes.

Ziegler[16] supposed that normally there was a sort of balance between the lymphatic and the myeloid tissues of the body, and he was able to cause myeloid metaplasia by destruction of the Malpighian bodies of the spleen. But the appearance of his specimens was not that of leukemia, and there is certainly no abnormality of lymphatic tissue in the early stage of myelosis.

Naegeli[12] supposes that leukemia is a disturbance of correlation, but presumes that the error is in the balance of the endocrine system. It may be admitted, that in the absence of a nerve supply, the regulation of the hematopoietic organs must be of chemical nature, but this could normally govern only the emigration of mature cells and the size of the functional organ, for example, bone marrow, but in leukemia there is a qualitative as well as a quantitative change which would require some other explanation. If such an endocrine disturbance be supposed to be the cause of leukemia it is an obvious corollary that the malady must affect the whole of the hematopoietic system—this is certainly not the case, as areas of normal blood-forming tissue can always be found, even in advanced cases, that is, not all the lymphatic or myeloid tissue is affected at the same time or to the same extent.

The view of von Hansemann, that an infective origin must be postulated because no other view will fit all the known phenomena, is thus not correct and, in fact, it might well be supposed that by a similar process of exclusion all conditions other than neoplasia might be excluded.

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HETEROTOPIA OF ADRENAL IN LIVER AND KIDNEY.*

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In its varying degrees heterotopia of the adrenal in the liver or kidney appears to be a much more common developmental disturbance than the literature upon the subject would lead one to expect. Four well-marked examples of this condition have appeared in the last 800 autopsies done in the Pathological Laboratory of the University of Michigan. Yet adrenal heterotopia in liver and kidney has been quite generally ignored in the monographical presentations of diseases of the adrenal and in systems of medicine. One of the most recent of these simply says that "One case, at any rate, has been reported in which the right suprarenal was found beneath the fibrous capsule of the kidney," and predicts that the future development of endocrinology may reveal further occurrences of such anomalies.

By definition, from the groups of adrenal-renal heterotopia and adrenal-hepatic heterotopia, forming the subject of this report, there must be excluded the accessory adrenals that may be found upon, in or beneath the capsules of these organs, and likewise there must be excluded the more or less undifferentiated tissues of nephros origin which may be found within the kidney, particularly, some of which come to resemble adrenal cortex. It is fully recognized

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that the different types of malposition which may be properly designated heterotopia may be in a sense a major degree of these conditions just excluded, but from every point of view, except the embryological one, they are fundamentally different. In the various types of inclusions and "rests" which we bar from this category by definition, an adrenal is to be found upon the same side. With heterotopia no adrenal other than the one included is to be found upon that side. To these dicta which appear so simple and so fundamentally sound there are at least three reported exceptions. One was briefly described by Grawitz,[2] another by Radasch,[7] while the third is a case described by Miloslavich,[4] in which there was a duplication of one adrenal so that, while there was apparently a true and complete unilateral adrenal-renal heterotopia, another well-formed adrenal was found upon the same side. Exceptions of this nature, involving complete duplication of the adrenal and a heterotopia of one of the resulting pair, must be rare, so that, in general, the presence of a well-formed adrenal in normal relationship is against, but does not entirely rule out, heterotopia of the adrenal on the same side.

The importance of the condition here described is more than an academic one. It is true that it probably will never be recognized except in the operating room and at autopsy, but its correct interpretation is of great importance both to the surgeon and to the pathologist. In a high grade of adrenal-renal heterotopia the surgeon will find it impossible to effect a separation of the two organs in doing a nephrectomy unless he dissects through renal tissue. He must bear in mind, also, the fact that the condition is often bilateral. If, either by acquired disease or by developmental failure, the remaining heterotopic adrenal is inadequate, death by adrenal insufficiency will ensue. Proper recognition of the gross and microscopic pathology of this condition as met at autopsy will guard the pathologist on the one hand against an erroneous interpretation of it as neoplastic or otherwise and, on the other, will inform him in respect to certain important aspects of the constitutional pathology of the cadaver upon which he is working.

Literature of Adrenal-renal Heterotopia. Rokitansky,[8] in 1846, had differentiated acquired inflammatory adhesion between the adrenal and renal capsules from true heterotopia which he characterized as exhibiting a common tunica albuginea investing the two organs. He gave no case report. Since Rokitansky, most of the important text-books of pathological anatomy have briefly referred to the renal type of adrenal heterotopia.

The first case report in the literature is that of Klebs,[3] in 1876, who recorded the occurrence of a thin yellowish layer spread beneath the kidney capsule at the upper end of each kidney. In the usual situations no adrenals were to be found, and microscopical examination showed the thin yellow layer to be made up of cells like those

of adrenal cortex. His patient was a well-developed male, aged twenty years, who died of pneumonia.

A briefly described observation published by Grawitz,[2] in 1884, came next in chronological order. In a girl, aged two years, adrenals as accessory or supernumerary organs were found at the upper pole of each kidney beneath the kidney capsule. The adrenals themselves were apparently in the normal situation. On the right a portion of the adrenal tissue extended to the depth of 1 cm. in a cleft between two neighboring renal lobules.

In the course of the autopsy of a male, aged sixty-seven years, who died as a result of a cardio-vascular-renal complex, Pilliet,[6] in 1893, found no trace of the right adrenal in its usual situation. On section of the kidney, however, a yellow plaque was found under the capsule at the upper part of the anterior convexity. Microscopical examination showed this to be adrenal and in some areas there was complete fusion of the two parenchymas. The structure had the appearance of being half of the adrenal only, being made up chiefly of cortical substance, although large bloodvessels, bundles of plain muscle and atrophic groups of medulla cells were found in areas.

In 1895 there were two papers reporting 3 cases of the renal type of adrenal heterotopia. Weinberg[12] recorded an instance in a woman, aged fifty-four years, who died in coma. In attempting to decorticate the kidneys, the renal capsules were found to cover partially a substance identified as adrenal. The right adrenal was united with the kidney for a distance of 3 cm. The left adrenal was united with the left kidney for a distance of 1.5 cm. The remaining portions of the adrenals were free and had the appearance of being enclosed within diverticula of the kidney capsules. Microscopically the adrenals were found to have their own delicate capsules which were lacking completely at certain areas where the parenchyma of the adrenal was in immediate contact with the cortical substance of the kidney. Renal and adrenal tissues were found "côte à côte, parfois se mélangent, mais ne présentent pas d'anastomoses entre eux." No chronic inflammatory changes were found in the kidneys.

In the same year there appeared Ulrich's[10] important paper on misplaced and accessory adrenals in which two examples of adrenal-renal heterotopia were included. The first of these was in a male, aged seventy-two years, alcoholic and demented, who died an asphyxiative death following aspiration. Both adrenals were found spread out in a thin sheet, from 0.5 to 1 mm. in thickness, over the upper poles of their respective kidneys. Upon attempting to remove the kidney capsule, the adrenal was in part removed with it and in part remained adherent to the kidney. No adrenals were to be found in their usual situation. On microscopical examination, a layer of adrenal cortex about 1 mm. thick was found

over the surface of the kidney and separated from it in certain areas only by a connective tissue layer of similar thickness. In some areas the three cortical zones could be recognized, in others only the zona fasciculata. No medullary substance was found. In those areas in which no connective tissue intervened between the two organs, adrenal tissue was found in close association with the urinary tubules.

The second patient of Ulrich's was a male, aged sixty years, diagnosed as a case of psychosis secondary to advanced pulmonary tuberculosis. This the author characterizes as an example of *dystopia partialis glandularum suprarenalium*. The right adrenal consisted of two connected portions, of which the larger was in the form of a flattened mass applied to the anterior aspect of the upper pole of the kidney. The smaller portion was above and apart from the kidney and appeared to be composed chiefly of medulla. Upon stripping off the kidney capsule, the flattened portion of adrenal was found to be left behind, nor was there any loss of substance from the surface of the adrenal from which the kidney capsule came away smoothly. At its inner side the adrenal tissue was found to mingle somewhat with the renal tissue, in such areas no visible connective-tissue capsule intervening. The total thickness of the sheet of adrenal tissue was 1.5 mm. On microscopical examination the zona reticularis was found to be directly upon the surface of the kidney in certain areas and the intimate intermingling of renal and adrenal tissue was fully verified. No medullar tissue was found in this portion of the adrenal. The left adrenal presented in general the same appearances, but was not so intimately united with the kidney.

In 1902 Radasch[7] reported an interesting case of adrenal heterotopia which probably should be included in our present list. Autopsy verified a clinical diagnosis of gumma of the brain in a male, aged twenty-nine years, who died following a cerebral decompression operation. The kidneys were found to be of normal size. Upon the anterior-superior surface of each kidney a thin yellowish body was found. Each of these covered an irregular area about 3 cm. in diameter and about 1 mm. thick. They were beneath the capsule and in places dipped into the renal cortex. An adrenal of normal size and shape and in the usual location was present on the right side only. Upon the under surface of the liver near the transverse fissure a small, thin, yellowish mass was noticed. It resembled those upon the kidneys and was approximately 1 cm. in diameter and 2 mm. thick. Histological examination of the adrenals in the kidneys showed all three cortical zones with an incomplete capsule between the adrenal tissue and the renal tissue and an intimate mixture of the two parenchymas. Microscopical examination of the mass on the liver showed this also to be adrenal tissue but the relationship was much less intimate, for a thick

layer of loosely arranged connective tissue containing oval masses of adrenal cells separated it from the liver. The reticular zone appeared to be external. The medulla is not mentioned in respect to either situation. Disregarding the hepatic adrenal tissue, which is difficult to interpret from the description, this would appear to be a true instance of bilateral adrenal-renal heterotopia with right unilateral duplication of the adrenal. The presence of additional adrenal tissue on the under surface of the liver serves to connect the cases we are describing with the more common type of aberrant adrenal masses.

Miloslavich[4] made the most important contribution thus far to the casuistry of adrenal heterotopia in his paper of 1914. In this he added four new examples, reviewed much of the earlier literature and discussed the general significance of developmental disturbances of the adrenal from the standpoint of constitutional pathology. His first patient was a male, aged twenty-three years, who died a respiratory death from bulbar paralysis due to a diffusely infiltrating glioma of medulla, pons and cerebellum, nearly filling the fourth ventricle. There was a marked hyperplasia of all lymphoid tissue and a two-lobed thymus was present. The right adrenal was in the form of a nearly circular disk, measuring 6.5 by 5.5 cm., which was applied to the anterior surface of the upper pole of the kidney. In the central portion this disk was thinned out to such a degree that the adrenal tissue appeared in the form of small isolated islands, while at the circumference of the thinned portion a broad continuous ring of adrenal parenchyma, 0.5 to 1 cm. wide, was present. The left adrenal showed the same changes, but to a somewhat slighter degree. No microscopical description of this case is presented.

His second patient was a male, who died when forty-seven years of age, with a clinical diagnosis of diabetes mellitus and myocardial degeneration. While the thymus was represented by a well-defined fatty mass only and did not appear lymphoid, all other lymphoid structures showed the marked hyperplasia of a status lymphaticus of high degree. The adrenals had the form of nearly circular disks, 5 to 6 cm. in diameter, firmly fixed at the upper pole of each kidney. On removing the kidney capsules the adrenal tissue was left attached to the kidney. On section, the adrenal was found to be very thin, measuring only 1 mm., the lower cortical leaf could scarcely be recognized as such, no limiting layer (capsule) could be found and medullary substance was not recognizable. On microscopical examination the single cortical layer was found to show its three zones well differentiated. In areas it was separated from the kidney parenchyma by a delicate connective-tissue layer which was interrupted entirely for varying distances where the parenchyma of the adrenal came in direct contact with kidney elements. In some sections the adrenal cell

complexes which were mingled with kidney tissue resembled those of the zona glomerularis while others were of the type of the zona fasciculata. The medulla was very sparsely represented by single cells or small groups of cells. The left adrenal showed similar microscopical findings. Rounded and elongated masses of smooth muscle were found in and beneath the kidney capsule, where adrenal and kidney were united, in the zona glomerulosa lying in the kidney and in the central portion of the adrenal.

The third case contributed by Miloslavich was that of a man, aged twenty-six years, with a clinical diagnosis of tuberculous meningitis, found at autopsy to have chronic pulmonary and generalized miliary tuberculosis. There was a persistent hyperplastic thymus, measuring 7 cm. in length and 3 cm. in breadth, and a small thyroid. The left adrenal was broad and thin and united with the upper pole of the kidney. The right kidney was large and presented a double pelvis and double ureters which were united at the level of the brim of the pelvis. The right adrenal was somewhat larger than the left and was attached not only to the upper pole of the kidney but also to the liver. Between the right adrenal and the kidney there was no demarcating connective-tissue layer, while on the left a recognizable separation was present. Between the right adrenal and the liver a slender connective-tissue layer effected a separation. Microscopical examination showed between the right kidney and adrenal a thin connective-tissue layer which became more and more attenuated until it was entirely lacking over extensive areas, permitting the two types of parenchyma to come into immediate contact. Between the left kidney and left adrenal the intervening capsule showed only small defects, and the capsule between the right adrenal and the liver was everywhere continuous. The cortical zones of both adrenals were easily recognizable, but the medullary substance, especially in the right, could not be differentiated with certainty.

The fourth case described by Miloslavich was placed apart from his detailed series, and will be seen to fall into a different category. It should be included here, however, as of importance in establishing one of the varieties of renal-adrenal heterotopia, and should be grouped with the examples from Grawitz and Radasch given above. A woman, aged forty-six years, who died of pulmonary tuberculosis, showed at autopsy a small thyroid, kidneys and adrenals in normal position with the left adrenal closely applied to the kidney and, beneath the capsule of the left kidney, another adrenal measuring 4 by 3 cm. and about 2 mm. thick. There was a plain differentiation of cortex and medulla. No microscopical notes are given. We are not told to what degree the parenchyma of one organ was mingled with that of the other, and no mention of thymus or lymphatic system is made.

More recently (1920) Apert and Vallery-Radot[1] have reported a

typical example of bilateral adrenal-renal heterotopia in a boy, aged six years, who died of tuberculous meningitis. The adrenals were situated anteriorly on the upper poles of the kidneys. Their anterior faces were smooth and they could be distinguished from the kidney substance practically by color alone. Microscopical examination showed a partial admixture of the parenchyma of the two organs and no medullar tissue was found. The thymus was not mentioned.

Literature of Adrenal-hepatic Type. Weiler,[11] in 1885, reported the occurrence of the right adrenal upon the convex portion of the surface of the liver, at a distance of but 3 cm. from the fold of the right coronary ligament. From the posterior portion of the main mass a more slender prolongation extended through the capsule and into the substance of the liver to a depth of 5 mm. There was also a close union between the left adrenal and left kidney, the adrenal being situated between the layers of the fibrous capsule of the kidney. The patient was a male, aged twenty-five years, who died of pulmonary tuberculosis.

The case reported by Schmorl,[9] in 1891, which is considered by Miloslavich as belonging with those in which the entire adrenal is found in or beneath the hepatic capsule, has been misquoted by the latter. It is evident that the masses of adrenal tissue which in this instance were separated from the hepatic parenchyma only by an incomplete septum through which bile ducts could be traced were relatively small accessory adrenals, while the organ proper was found in its usual situation. This case must therefore be excluded.

In 1900, in the course of an autopsy on a female infant, aged one year, Oberndorfer[5] found the right adrenal adherent in the impressio suprarenalis and apparently separated from the liver by a band of connective tissue about $\frac{1}{3}$ mm. wide. The capsule was thickened. There is no evidence that the parenchyma of one organ was mingled with that of the other. The child exhibited a hypertrophic liver cirrhosis of syphilitic origin. The author, probably rightly, attaches much importance to the chronic inflammatory process in explaining the etiology of the condition. He suggests that there may have been a primary inclusion of the adrenal, with secondary separation of the two organs through connective-tissue proliferation in connection with the cirrhosis; or that through connective-tissue proliferation certain groups of cells may have been snared off and thus come more and more to lie in the accumulating connective tissue between the two organs. He favors the second explanation. In view of the demonstrated inflammatory condition present, this case must be included with reservations, if at all.

To the examples appearing in the literature we are able to add cases falling into each of the two main groups—1 to the group of 12 cases of adrenal-renal heterotopia and 3 to the 1 or 2 hitherto

TABULAR SUMMARY OF THE PREVIOUSLY REPORTED CASES OF BOTH TYPES OF ADRENAL HETEROTOPIA WITH ADDITION OF THE NEW CASES DESCRIBED IN THE PRESENT PAPER.

	Author.	Date.	Heterotopia.	Duplication	Sex.	Age.	Remarks.
1	Klebs	1876	Bilateral adrenal-renal	None	M.	20	Pneumonia.
2	Grawitz	1884	Bilateral adrenal-renal	Bilateral	F.	2	Cause of death not given.
3	Pilliet	1893	Right adrenal-renal	None	M.	67	Cardiovascular renal death.
4	Weinberg	1895	Bilateral adrenal-renal	None	F.	54	Death in coma.
5	Ulrich	1895	Bilateral adrenal-renal	None	M.	72	Alcoholic. Demented. Asphyxiative death.
6	Ulrich	1895	Bilateral adrenal-renal	None	M.	60	Psychosis. Tuberculosis.
7	Radasch	1902	Bilateral adrenal-renal	Right	M.	29	Gumma of brain.
8	Miloslavich	1914	Bilateral adrenal-renal	None	M.	23	Thymico-lymphatic constitution. Glioma of pons.
9	Miloslavich	1914	Bilateral adrenal-renal	None	M.	47	Status thymico-lymphaticus. Diabetes.
10	Miloslavich	1914	Bilateral adrenal-renal	None	M.	26	Status thymico-lymphaticus. Tuberculosis.
11	Miloslavich	1914	Left adrenal-renal	Left	F.	46	Tuberculosis.
12	Apert and Vallery-Radot	1920	Bilateral adrenal-renal	None	M.	6	Tuberculous meningitis.
13	Weller	1924	Bilateral adrenal-renal	None	M.	40	Thymico-lymphatic constitution. Familial diabetes.
1	Weiler	1885	Adrenal-hepatic	None	M.	25	Pulmonary tuberculosis.
2	Weller	1924	Adrenal-hepatic	None	M.	25	Persistent thymus. Endocarditis.
3	Weller	1924	Adrenal-hepatic	None	M.	17	Persistent thymus. Lymphosarcoma.
4	Weller	1924	Adrenal-hepatic	None	M.	61	Persistent thymus. Empyema.

reported cases of adrenal-hepatic heterotopia (see Table I). For the sake of brevity the protocols of our cases have been abstracted and only the data germane to our present discussion will be quoted. In each instance these will appear in a definite order: Autopsy number; sex; age; clinical diagnosis; habitus of cadaver; gross pathology of brain, thyroid, thymus and lymphadenoid tissues in general, left kidney, left adrenal, right kidney, right adrenal; microscopical pathology of such of these organs as show significant changes; pathological diagnosis.

CASE I.—*Bilateral Adrenal-renal Heterotopia (without Duplication).* Autopsy No. 1559 (A–62–AB). E. W., male, aged forty years.

CLINICAL DIAGNOSIS. Diabetes mellitus; chronic pancreatitis.

HABITUS. Cadaver of slender build, exhibiting the asthenic constitution to a marked degree. (The patient comes from a family with an unusual history of severe familial diabetes.)

GROSS PATHOLOGY. *Brain:* no anomalies; no gliosis. *Thyroid:* small. *Thymus:* no thymic parenchyma recognized with the naked eye. *Left kidney:* in normal position and of normal size. *Left adrenal:* spread out in a thin sheet covering the upper pole of the left kidney, particularly anteriorly, and apparently having a common capsule with the kidney. *Right kidney:* normal in size and position. *Right adrenal:* in general, resembles the left and bears a similar relation to the right kidney, but covers a considerably greater portion of the kidney surface, occupying nearly one-half of the anterior aspect as it spreads downward from the upper pole; here, also, a common capsule appears to cover the united organs.

MICROSCOPICAL PATHOLOGY. *Brain:* congestion and edema only; no gliomatous proliferation or sclerosis in areas sectioned. *Thyroid:* marked diminution of colloid; many acini containing no colloid; cells more distinctly low columnar in type than in the normal thyroid, but no parenchymatous hypertrophy of the exophthalmic type; stroma increased, both relatively and absolutely. *Thymus:* abundant remains of thymus; numerous large and calcareous corpuscles of Hassall; atrophic hyperplastic thymus. *Lymph nodes:* marked exhaustion of germ centers. *Adrenals:* sections across the adrenals, including the upper poles of the kidneys, are alike, one description answering for those of both sides. At its upper surface the adrenal has a capsule of its own and at its border it exhibits a rounded edge. At this point it lies separate from the renal capsule for a distance of 2 cm. Leaving the free portion, the renal and adrenal capsules first fuse, then become attenuated, and finally disappear entirely in certain areas. A fused capsule reappears at intervals. Where the capsule is lacking there is an intimate admixture of renal and adrenal parenchymatous tissues, and for part of the distance that half of the adrenal cortex toward the kidney

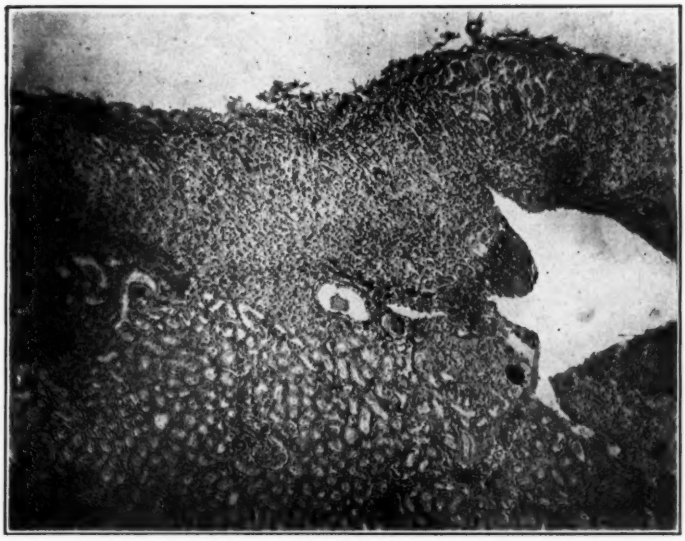

FIG. 1.—Case 1. Adrenal-renal heterotopia. Low-power photomicrograph showing reduction of adrenal to its outer cortical leaf only. This, and an adrenal vein as well, are in intimate contact with the renal parenchyma. (All photomicrographs were made from hemalum and eosin stained sections.)

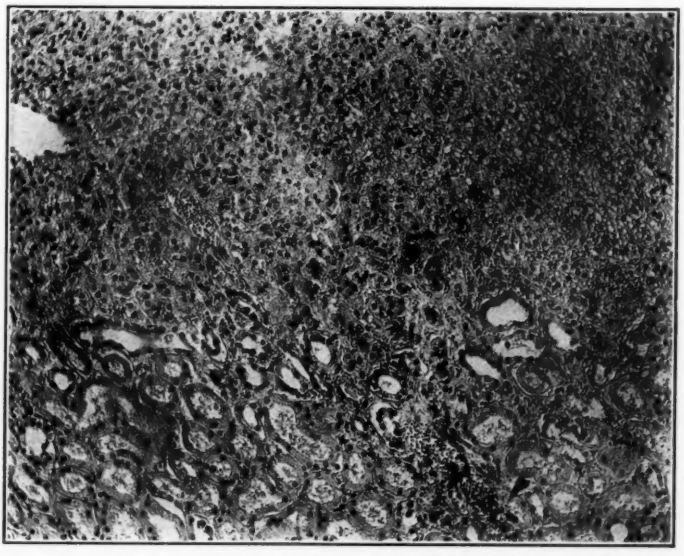

FIG. 2.—Case 1. Adrenal-renal heterotopia. Higher power photomicrograph to show the absence of any connective tissue capsule between the parenchyma of the kidney and that of the adrenal. Renal tubules lie against cords of adrenal cortical cells.

FIG. 3.—Case 1. Adrenal-renal heterotopia. Photomicrograph of an area which shows no limiting membrane between kidney tissue and adrenal. A large adrenal vein is very near the kidney parenchyma indicating the absence of that leaf of the adrenal cortex normally presenting toward the kidney.

FIG. 4.—Case 2. Adrenal-hepatic heterotopia. Low-power photomicrograph showing adrenal cortex and a large adrenal vein with coarse bundles of involuntary muscle in the upper part of the field. Small bile ducts and a large hepatic trinity are in immediate relationship with the adrenal tissues.

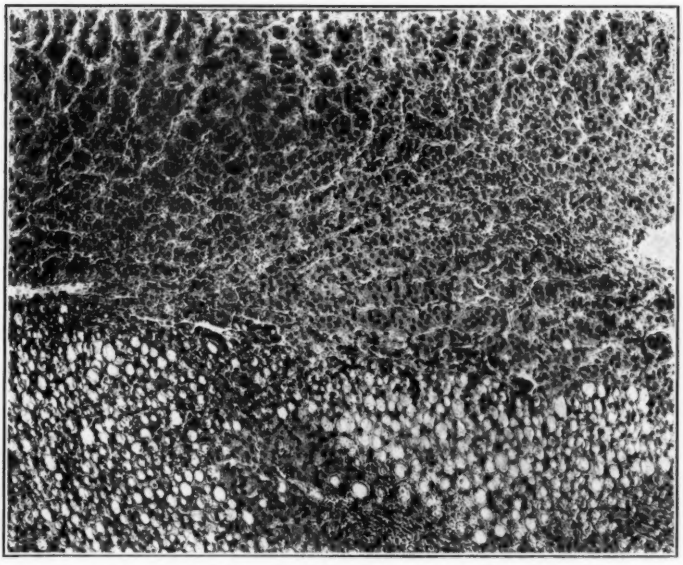

FIG. 5.—Case 3. Adrenal-hepatic heterotopia. Complete absence of any connective-tissue layer between the adrenal and the hepatic parenchyma. The hepatic tissue is sharply differentiated by reason of the fatty change present in it.

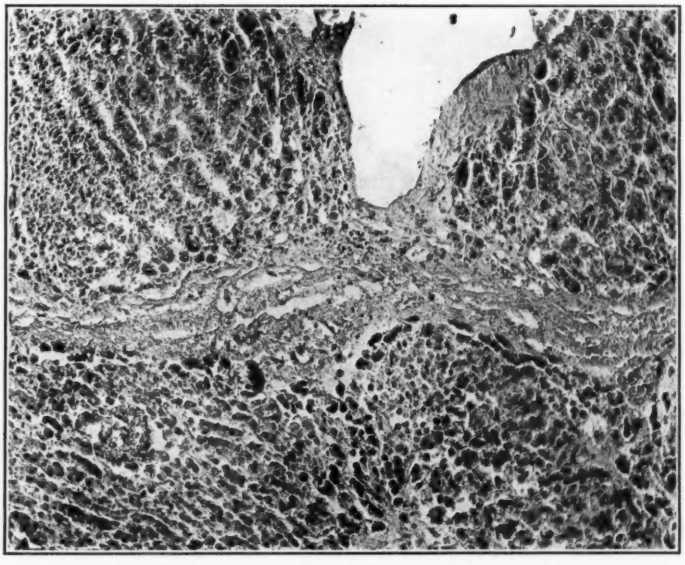

FIG. 6.—Case 4. Adrenal-hepatic heterotopia. This case shows a less marked degree of the condition, a few connective-tissue fibrillæ remaining between the two organs. This band appears wider than it should due to traumatic artefact. The proximity of the adrenal vein to liver tissue is proof of the developmental nature of the union between the two tissues.

disappears entirely, bringing the adrenal veins in direct relationship to renal tissue in some areas; while medulla is present in that portion of the adrenal having an independent capsule, through the remainder of the organ medulla is entirely absent; in the areas showing the most intimate admixture the adrenal is therefore represented only by the superficial half of its cortex, that is, the half of the cortex normally farther away from the kidney, and a fibrous capsule which now covers both organs; there is a well-marked lipoidosis of the adrenal cortical cells.

PATHOLOGICAL DIAGNOSIS. Chronic atrophic interstitial pancreatitis (pancreatic insufficiency, diabetes, steatorrhea); marked emaciation; serous atrophy of all adipose tissues; atrophic hyperplastic thymus; heterotopia of both adrenals, with hypoplasia and lipoidosis; pituitary hypoplasia or atrophy, with diminished eosinophile cells; generalized lymphoid exhaustion; hypothyroidism; asthenic constitution; acute staphylococcus serofibrinous pneumonia; multiple pyemic excretory abscesses of right kidney; multiple staphylococcus emboli; severe catarrhal gastro-enteritis; hypertrophy of intestinal musculature; old healed tubular nephritis; early sclerosis of renal arteries; moderate atherosclerosis of aorta; old focal leptomeningitis; atrophy, congestion and acute parenchymatous degeneration of all organs; lymphoid infiltration of periportal tissue; excessive hemolysis in spleen and lymph nodes; eosinophilia of prevertebral lymph nodes; diminished spermatogenesis.

CASE II.—*Adrenal-hepatic Heterotopia (without Duplication).* Autopsy No. 1118 (A–70–Y). L. D., male, aged twenty-six years.

CLINICAL DIAGNOSIS. Vegetative endocarditis (Streptococcus viridans) of aortic and mitral valves; aortic and mitral insufficiency; cardiac hypertrophy and dilatation; myocardial degeneration; embolism of spleen; parenchymatous nephritis.

HABITUS. Medium build; intercostal angle much greater than a right angle; type approaches that of the thymico-lymphatic constitution.

GROSS PATHOLOGY. Permission to examine the *brain* and neck organs (*thyroid*) was refused. *Thymus:* no lymphoid tissue recognizable in the thymic fat upon naked-eye examination. *Left kidney:* in normal position; somewhat larger than normal. *Left adrenal:* of normal size and in normal position; moderate lipoidosis of the cortex. *Right kidney:* normal in size and position. *Right adrenal:* upon attempting to remove the right suprarenal it was found to be firmly united to the posterior surface of the right lobe of the liver at the impressio suprarenalis; the usual easy separation between the two organs could not be effected; while the lower pole of the adrenal could be lifted slightly away from the surface of the kidney, the remainder of the gland was firmly fixed, its

capsule apparently uniting with the liver capsule and the greater part of the suprarenal gland substance appearing to be beneath the joint capsule of the two organs.

MICROSCOPIC PATHOLOGY. *Thymus:* persistent; fibroid atrophy but with numerous corpuscles of Hassall; an atrophic hyperplastic thymus. *Lymph nodes:* hyperplastic. *Right adrenal:* throughout the greater part of its length, the adrenal is firmly adherent to the liver, from which it is separated in some areas by a thin connective-tissue band, while in other areas there is no connective tissue intervening between the two organs; small bile ducts occur very constantly within the adrenal parenchyma; through much of the distance the adrenal is represented only by the glomerular, fascicular and reticular zones of its outer one-half; in a few areas only is there any medulla; the zona pigmentosa lies in immediate association with the bile ducts and liver cells of the hepatic parenchyma; along this line a large adrenal vein with its characteristic musculature is in immediate association with a large hepatic vein and bile duct.

PATHOLOGICAL DIAGNOSIS. Chronic aortic thrombo-endocarditis; Streptococcus viridans infection; rupture of aortic cusp; mycotic aneurysm in first portion of aortic arch; subacute pericarditis and myocarditis; aortic stenosis and insufficiency; relative mitral insufficiency; cardiac dilatation and hypertrophy; chronic passive congestion of lung with diffuse interstitial pneumonia; multiple infarctions of spleen and kidneys; nutmeg liver; chronic passive congestion of all organs; hydropericardium, hydrothorax, ascites; subacute parenchymatous nephritis with multiple embolic abscesses; serous atrophy of all fat tissues; fatty degeneration of intima of aorta; hepatic heterotopia of right adrenal; aspermatogenesis; melanosis of skin of thorax; secondary anemia; persistent thymus.

CASE III.—*Adrenal-hepatic Heterotopia (without Duplication).* Autopsy No. 1564 (A–67–AB). E. U., male, aged seventeen years.

CLINICAL DIAGNOSIS. Intestinal obstruction.

HABITUS. Tall slender type; long bones slender and long; intercostal angle much less than a right angle; asthenic constitution.

GROSS PATHOLOGY. Permission to examine the *brain* was refused. *Thyroid:* about normal size; abundant colloid substance; no adenomas. *Thymus:* thymic parenchyma was not recognized as such with the naked eye. *Left kidney:* normal in size and position. *Left adrenal:* normal in size and position. *Right kidney:* normal in size and position. *Right adrenal:* upon attempting to remove the right adrenal it was found to be firmly united to the posterior surface of the right lobe of the liver at the suprarenal impression. The usual easy separation between the two organs could not be effected; only the lower pole of the adrenal could be lifted from the

surface of the liver, a common capsule apparently covering the two organs.

MICROSCOPIC PATHOLOGY. *Thyroid:* excess of colloid substance. *Thymus:* abundant thymic remains with large corpuscles of Hassall; must be considered a hyperplastic thymus. *Right adrenal:* at its free border the right adrenal has a complete but thin capsule of its own, and in this portion medulla is present within characteristic cortical zones; at first becoming a common band of connective tissue between the two organs, this portion of the capsule finally disappears entirely, leaving hepatic and adrenal parenchymas in intimate contact with each other; in this portion no medulla is present—in fact, where the union is most complete the inner half of the cortex, that is, the portion adjacent to the liver normally, has entirely disappeared.

PATHOLOGICAL DIAGNOSIS. Primary intestinal lymphosarcomatosis, involving jejunum in greatest degree, with stenosis and dilatation of portion of jejunum; diffuse peritoneal lymphosarcomatosis; diffuse lymphosarcomatous infiltration of mesentery and retroperitoneal adipose tissues; general marasmus; tiger heart; fatty infiltration of liver; cloudy swelling of kidneys; hepatic heterotopia of right adrenal; hypertrophic thymus; asthenic constitution; colloid goiter; total aspermatogenesis; atrophy, passive congestion and parenchymatous degeneration of all organs.

CASE IV.—*Adrenal-hepatic Heterotopia (without Duplication).* Autopsy No. 1603 (A–106–AB). P. L., male, aged sixty-one years.

CLINICAL DIAGNOSIS. Pneumonia; empyema; auricular fibrillation; hypertrophy of prostate.

HABITUS. Long slender build; long bones long and slender; thorax long but intercostal angle is slightly greater than a right angle; asthenic constitution.

GROSS PATHOLOGY. *Brain:* negative except for congestion and edema. *Thyroid:* somewhat larger than normal; both colloid and stroma increased; adenomatous areas. *Thymus:* represented by a long strip of fatty tissue only. *Left adrenal:* moderate hypoplasia; increased pigmentation of the zona pigmentosa. *Left kidney:* in normal situation. *Right adrenal:* the right adrenal was found to be firmly united to the under surface of the right lobe of the liver at the impressio suprarenalis and could not be removed apart from the liver; the adrenal capsule appeared to be continuous with that of the liver. *Right kidney:* in normal situation.

MICROSCOPIC PATHOLOGY. *Brain:* edema and postmortem change only. *Thyroid:* colloid goiter; colloid cysts; increase of stroma locally; connective tissue hyaline change and calcification in the stroma. *Thymus:* abundant lymphoid remains of thymus with numerous corpuscles of Hassall; atrophic hyperplastic thymus. *Lymphoid tissues:* no marked hyperplasia. *Left adrenal:* hypoplasia

of both cortex and medulla; medulla substance present in fair amount. *Right adrenal:* a thin connective-tissue capsule common to adrenal and liver is found to intervene between the parenchymatous portions of these two organs; in areas this connective-tissue band becomes reduced to the width of three or four coarse connective-tissue fibers, and into these, cords of liver cells extend; there is no intermingling of the parenchyma of the organs; the branches of the adrenal vein approach this connective-tissue band with no adrenal cortex intervening; in the portion of the adrenal in closest relationship to the liver there is no medulla; as the organ becomes separated from the liver capsule by intervening adipose tissue a hypoplastic medulla appears; the entire organ is hypoplastic.

PATHOLOGICAL DIAGNOSIS. Chronic bilateral empyema, encapsulated on the right side; chronic purulent bronchopneumonia; atelectasis; emphysema; multiple calcified tubercles in lungs and bronchial nodes; aortic atherosclerosis; atrophy, fibrosis and dilatation of heart; coronary sclerosis; chronic purulent prostatitis with fibrosis; chronic hyperplastic cystitis; chronic parenchymatous nephritis with multiple cysts; atrophy and passive congestion of all organs; chronic perisplenitis and perihepatitis; adenomatous colloid goiter; atrophic hyperplastic thymus; adrenal hypoplasia; hepatic heterotopia of right adrenal; dislocation of left shoulder.

Discussion. With our own cases added, we have for analysis 13 cases of adrenal-renal heterotopia and 4 cases of adrenal-hepatic heterotopia, excluding the doubtful case of Oberndorfer. We find at once that the proposed test by which to check the genuineness of this condition, namely, the absence of the adrenal from its usual situation fails us, for in 3 otherwise acceptable cases, those of Grawitz,[2] Radasch[7] and the fourth Miloslavich[4] case, there had been a duplication of the adrenal so that a gland was present in the normal situation. Moreover, these 3 cases complicated by duplication are of three distinct types. The example from Grawitz exhibited a bilateral adrenal-renal heterotopia and a bilateral duplication; that from Radasch, a bilateral heterotopia and a right unilateral duplication; that from Miloslavich, a left unilateral heterotopia and duplication. The other possible combinations will doubtless be discovered and described in course of time.

It is evident, therefore, that while the absence of an adrenal in the normal situation is of value in determining a true heterotopia, the presence of one still leaves open the possibility of heterotopia associated with duplication. In such a case the further test may be applied of requiring the heterotopic adrenal to present the general form and organization of an adrenal. This will exclude the accessory adrenal masses, usually more or less rounded in form, and frequently of small size, which cannot be considered adrenals proper. It is fully appreciated, however, that this distinction is somewhat arbitrary and that there are cases in the

literature occupying a middle ground and indicating that the heterotopic adrenal with complete duplication is but a grosser manifestation of that dissemination which makes it possible to find small accessory adrenals, usually composed of cortex only, in practically every cadaver in which careful search for them is made.

The bilateral adrenal-renal heterotopia is so conspicuous at autopsy and so easily recognized and interpreted that it is clear that the small number (13) of reported examples must be due to the fact that it is a relatively rare condition. It is usually bilateral, this being true of 11 of the 13 cases. It appears to affect males, especially, 10 of the 13 cases having been of that sex. One of the 2 unilateral cases was in a female, as were also 2 of the 3 cases associated with duplication of the adrenal.

Adrenal-hepatic heterotopia, on the other hand, especially in its less complete degrees, might easily be overlooked at autopsy. That we have been able to find but 1 positive case in the literature cannot be interpreted as demonstrating the extreme rarity of this condition. It is more probable that it has been overlooked, or when found, has not been considered of sufficient importance to merit report. That we have found 3 examples of this condition in the last 800 autopsies supports this view. Here, again, the condition seems to be one affecting males particularly, the questionable case of Oberndorfer[5] being the only one in a female in this group. With the total number so small, however, no firm conclusion on this point can properly be drawn.

Certain anatomical considerations are of interest. The degree of inclusion of the adrenal may vary over the widest limits, from union of the capsules of the two organs to complete inclusion of the parenchyma of the adrenal beneath the capsule of liver or kidney, bringing the parenchymatous structures of the two in immediate relationship, no capsular structure intervening and typical renal tubules or bile ducts, as the case may be, mingling with cords and nests of adrenal cortical cells. When the union is intimate a portion of the adrenal is usually wanting, so that only one leaf of the cortex is commonly found, showing its three layers of which the glomerular zone will be found to be outermost and the reticular zone mingling with the foreign parenchyma with which it is in contact. Medulla is either entirely wanting or is much reduced where the union is close, but the free poles of the same adrenal may show abundant medullar tissue. Large veins with accompanying bundles of involuntary muscle, characteristic of the adrenal, may be found in contact with the foreign parenchyma even when no adrenal medulla cells occur in the same region. In adrenal-hepatic heterotopia liver veins of considerable size may occur in such close proximity to these adrenal veins that it seems probable that some circulatory communication must exist.

It is not within the scope of this paper to discuss the embryology

of adrenal heterotopia. Attention is called, however, to the fact that the union or inclusion must take place early in development, since the partial or complete lack of medulla in many cases indicates that the medulla cells had not migrated into the cortical mass at the time the heterotopia occurred. True adrenal heterotopia in the sense in which the term is here used is a developmental condition. An acquired inflammatory adhesion of the adrenal to either kidney or liver is sometimes noted, and may result in dragging the adrenal somewhat out of its normal position. This probably explains the case of Oberndorfer[5] which we have accordingly excluded from our list. His patient was suffering from congenital syphilitic hepatitis. Such inflammatory conditions must not be mistaken for the developmental condition.

The most important aspect of adrenal heterotopia is its bearing upon constitutional pathology. Only Miloslavich[4] has hitherto seen the importance of this side of the question. The earlier writers give us very little information as to bodily habitus, the lymphatic apparatus and the brain, but the cases of Miloslavich and those which we add show how strikingly this condition is linked with the thymico-lymphatic constitution. Every one of our 4 cases had a persistent thymus as did the 3 of Miloslavich in which the thymus is mentioned. This must be interpreted in the light of the same organ interrelationships as the constant finding of a well-marked adrenal hypoplasia, usually affecting the medulla more than the cortex, in all those possessing the thymico-lymphatic constitution. By the same constitutional pathology is to be explained the relatively early deaths of cases of adrenal heterotopia. In our list we find deaths at ages of two, six, seventeen, twenty, twenty-three, twenty-five, twenty-six and twenty-nine. Only 4 of the 17 reached the age of sixty. These individuals have died at an early age because of their pathological constitution which entails increased susceptibility to infection and decreased resistance to extrinsic factors which prove lethal to them but not to the normal individual. When the chief causes of death are investigated we accordingly find a high incidence of infection, especially of tuberculosis, which is mentioned in 5 instances, with 2 cases of pneumonia, including empyema, and 1 of endocarditis. The one case of generalized lymphoblastoma may, from a broad biological point of view, be related to the constitutional pathology, as may also the glioma of the pons and the 2 cases of diabetes as explained below. We are left with but 4 or 5 cases in which the cause of death may not, in the present state of our knowledge, be at least remotely related to the pathological constitution.

From the evidence at hand it appears that the physical habitus of those with adrenal heterotopia is usually of the asthenic type. This in no sense is in contradiction to the evidence of the thymico-lymphatic constitution afforded by the thymus and by the lymph-

adenoid apparatus, for such a bodily habitus is frequently associated with that constitution and by some is included with it.

Miloslavich[4] was impressed by the fact that when various malformations of the adrenal were studied the developmental interrelationship between brain and adrenal became evident in the large proportion of associated cerebral conditions, particularly brain tumors and brain hypertrophy. Our cases offer no further evidence along this line. That important disturbances of metabolism of endocrinal origin may be associated seems clear. It must be more than a mere coincidence that the list includes 2 cases (Miloslavich, Weller) of fatal diabetes in males aged forty and forty-seven years. Our case came from a family in which other deaths from diabetes in siblings had occurred. This association of bilateral adrenal-renal heterotopia with diabetes should be watched for and made the subject of report. It is possible that a distinct type of diabetes may be present in certain of those in whom adrenal heterotopia is but one indication of a pathological constitution. In our case there were marked changes in the pancreas as well.

The renal type of adrenal heterotopia is of importance to the surgeon, since knowledge of the occurrence of this condition might make it possible for him to spare the adrenal in nephrectomy when otherwise it would be inevitably removed. Notwithstanding the fact that the adrenal is occasionally removed with the kidney in doing a nephrectomy and no ill-effects result, it would seem wise to preserve the heterotopic adrenal for the patient. Such an adrenal is usually, if not always, hypoplastic, particularly in respect to its medulla, and the condition is almost always bilateral. Both adrenals might be necessary to guard against adrenal insufficiency.

The hepatic type of adrenal heterotopia is much less apt to concern the surgeon. The union usually occurs in the impressio suprarenalis and therefore is away from the operative field in gall bladder or duodenal surgery. In view of the wide dissemination of smaller masses of adrenal cortical cells over the liver, and of the case reported by Weiler,[11] it is evident that a heterotopic adrenal may be found elsewhere than in the situation mentioned and may be encountered in surgical procedures.

Summary. 1. By heterotopia of the adrenal in liver and kidney is understood the developmental inclusion of the adrenal in or beneath the capsule of one of these organs. Inflammatory adhesions and the lesser aberrant adrenal masses are not included in this definition. Duplication of the adrenal may be present.

2. Of adrenal-renal heterotopia 1 new case is added. This condition occurs chiefly in males and is usually bilateral.

3. Three new cases of adrenal-hepatic heterotopia are added. Although presumably the more common of the two, this has received but little mention in the literature.

4. Adrenal heterotopia is usually associated with a persistent

thymus and other evidences of the thymico-lymphatic constitution, and frequently with the asthenic habitus. It is an evidence of constitutional pathology. Two of the 13 renal cases reported have died of diabetes. In accord with what is known of this constitution, most of the cases of adrenal heterotopia have died at a relatively early age. The incidence of tuberculosis and other infections is high.

5. In adrenal-renal heterotopia the surgeon will inevitably remove the adrenal in doing a nephrectomy unless special precautions are taken. Due to the medullar hypoplasia usually present and the bilateral nature of this condition, it may be especially important that the heterotopic adrenal should not be removed.

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THE PRIMARY MENINGEAL FORM OF SYSTEMIC BLASTOMYCOSIS.

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Systemic blastomycosis, the first case of which was reported by Busse and Buschke in 1894, is now recognized as a definite pathological and clinical entity. At the fastigium a typical case is not difficult to recognize, or at least to suspect. The outstanding features are essentially those of pyemia. There is usually an irregular fever accompanied by chills and sweats. The skin and

subcutaneous tissues are often extensively undermined by numerous large abscesses. Involvement of the osseous system is common and frequently widespread. Pulmonary implication is usually an early and characteristic feature, the persistent cough producing large amounts of purulent, often blood-stained, sputum. Pus or sputum mixed with 20 per cent potassium hydroxide will usually reveal the blastomycetes, which appear as yeast-like, double-contoured, budding organisms.

Necropsies have amply demonstrated the systemic nature of the infection, and have also shown that certain organs or systems are more prone to extensive involvement than others. This widespread dissemination is characteristic, and the metastases are now believed to occur principally through the blood stream. In view of these facts it is particularly interesting to note that the brain and meninges, especially the latter, are rarely implicated in the process.

The purpose of the present paper is two-fold: (1) To emphasize the infrequency of meningeal invasion, already commented on by other writers; and (2) to point out a small group of cases, to which the writer will add one of his own, which should be considered *clinically* as the *primary meningeal form of systemic blastomycosis*. In order to substantiate more forcibly the difference between ordinary systemic blastomycosis, with or without meningeal involvement, and the latter type it will be necessary to briefly analyze systemic blastomycosis with particular reference to the onset and the organs involved at autopsy. For this purpose 33 cases of systemic blastomycosis have been selected from the literature, all of which are corroborated by autopsy studies. This small group by no means exhausts the literature on the subject, but is believed to present a fairly accurate, composite picture of the condition.

A. Systemic Blastomycosis.[1–24] 1. *Onset or Primary Location.* Stober,[25] in a critical study of the condition, states: "It is generally held at the present, from both the clinical and pathological evidence, that the respiratory tract is the atrium of infection in systemic blastomycosis." He also suggests that the cutaneous lesions, which so often initiate the process, are very likely metastases from unrecognized pulmonary foci. He believes that the reversal of this channel of invasion, that is, systemic blastomycosis following the primary cutaneous form, is quite rare, since he finds only 3 cases in which it has been definitely proven.

Among the 33 cases selected for analysis in this paper, 27 (81.8 per cent) began with either pulmonary or cutaneous manifestations (20 pulmonary, 7 cutaneous). In the remaining 6 cases the primary symptoms were not stated in 1; consisted of vague joint symptoms in 3; abdominal pain, vomiting and ascites in 1; a diffuse rapidly spreading infection around a tooth in 1.

2. *Organs Involved at Autopsy.* A statistical study of the organs found involved at autopsy is the most direct route to a reconstruction, *en masse,* of the clinical course of these cases. The results from the 33 cases under discussion are shown in Table I. The importance of skin lesions, from small single pustules to large subcutaneous abscesses, is verified when we see that they were present in 32 out of 33 cases. The 1 case in which skin lesions were absent was atypical in other respects;[16] the antemortem symptoms were principally abdominal, and postmortem examination revealed involvement of the peritoneum but not of the lungs.

TABLE I.—ORGANS INVOLVED AT AUTOPSY IN THIRTY-THREE CASES OF SYSTEMIC BLASTOMYCOSIS.

Organ.	No. of cases.	Per cent.	Organ.	No. of cases.	Per cent.
Skin	32	97	Other bones or joints	17	51
Lungs	30	90.9	Peritoneum	1	3
Kidneys	15	42	Prostate	5	15
Liver	12	36	Testicle	1	3
Myocardium	3	9	Eye	2	6
Endocardium	1	3	Brain	9	27
Pericardium	4	12	Meninges	4	12
Spleen	19	57	Larynx and trachea	3	9
Pleura	7	21	Adrenals	2	6
Lymph glands	11	33	Gastro-intestinal tract	3	9
Pancreas	3	9	Spinal cord	2	6
Vertebra	9	27	Urinary bladder	1	3
Skull bones	7	21			

Next in importance and frequency are the lung lesions, which were present in 30 cases. Granting that the lungs were carefully searched for specific lesions in each instance, we must either assume that the organisms can gain entry through the respiratory tract and be disseminated throughout the body without producing permanent pathological changes in the lungs, or that there are other portals of entry.

Twenty-two cases (66.6 per cent) showed bone lesions involving either the vertebræ, skull or appendicular skeleton. Involvement of the skull bones is of particular interest because of its etiological relationship to meningeal invasion.

Involvement of the abdominal organs is very common and widespread, but actual invasion of the peritoneum, *per se,* is one of the rarest of lesions.

Brain lesions, usually abscesses, were present in 9 cases (27 per cent).

B. Systemic Blastomycosis with Meningeal Involvement. Among the 33 cases of generalized blastomycosis analyzed above, only 4 (12 per cent) were characterized by meningeal invasion.[26 27 28 29] These cases deserve special mention, and are analyzed separately in order to emphasize the differences between them and the small group in which blastomycotic meningitis occurred without gross

clinical evidence of systemic invasion. The brain and meninges were not examined in all cases of this series, but where clinical evidence of meningitis was not present we are fairly safe in assuming its pathological absence; the figure, however, may be somewhat low on this account.

1. *Onset, or Primary Location.* Two cases began with pulmonary symptoms and proceeded to run the typical course of generalized blastomycosis until the signs of meningitis occurred. One case began with a small pimple near the external canthus of the eye, which finally opened and discharged considerable pus. There was marked edema around the eye and the initial lesion. The fourth case is said to have started around a lower wisdom tooth. A gradual swelling of the whole face occurred, which became so marked that the patient could hardly open his mouth. Some time later the orbit became involved and an enucleation was performed.

2. *Organs Involved at Autopsy.* Table II gives the results of autopsy examination in these 4 cases. The systemic nature of the invasion is confirmed by a study of the organs involved, and only certain features deserve special emphasis. *Every case was characterized by some form of cutaneous lesion. Three cases showed pulmonary lesions and 3 cases had involvement of the skull bones.*

TABLE II.—ORGANS INVOLVED AT AUTOPSY IN FOUR CASES OF SYSTEMIC BLASTOMYCOSIS WITH MENINGEAL INVOLVEMENT.

Organ.	No. of cases.	Per cent.	Organ.	No. of Cases.	Per cent.
Skin	4	100	Brain abscesses	2	50
Skull bones	3	75	Heart (endo-, myo- and pericardium)	1	25
Paranasal sinuses	1	25	Spleen	2	50
Retropharyngeal abscess	1	25	Liver	1	25
Lungs	3	75	Eye	1	25
Vertebra	1	25			
Other bones or joints	2	50			

In reviewing this brief analysis of systemic blastomycosis, it is apparent that meningeal invasion is not as common as would be expected from the extensive nature of the metastases. Where meningeal invasion has occurred lesions of the skull bones or foci around the head have often facilitated direct invasion by continuity, or short metastases by way of the regional vascular and lymphatic channels.

C. Blastomycotic Meningitis without Clinical Evidence of Systemic Invasion. Six cases are analyzed under this heading—5 found in the literature and 1 case of the writer, not previously reported.

Case Reports. CASE I.[30]—A woman, aged sixty-three years, who after a period of general feebleness became confused and talkative, was admitted to the Matteawan State Hospital. During two weeks' observation she was in an almost continuous coma-

tose state, with occasional periods of low delirium. At autopsy the brain showed a diffuse pial haziness, more marked over the base than over the cerebrum. The meninges, particularly over the base, showed a remarkable appearance. The organisms were frequently found in large masses or scattered singly, and were more or less mixed with the elements of inflammatory exudate—lymphoid, plasma cells and large numbers of giant cells—which contained the organism. In the lateral ventricles the organism was found with accompanying exudate. Over the base where the reaction was most marked there was no tendency to tubercle formation or caseation. Near the root of the left lung there were numerous cavities filled with a gelatinous mucoid material. This was at first thought to be a colloid carcinoma, but it was later found that the gelatinous masses consisted of the typical large-capsuled budding organisms. *There were no skin lesions. All other organs were negative both grossly and in sections.*

CASE II.[31]—A Chinaman, aged fifty-three years, complained of severe and persistent headache which had been continuous for five weeks. The only other complaint was of failing vision. There was no history of any affection of the skin or of any lung trouble. The pupils were active and equal; the reflexes equal and active; there was no ataxia. The urine was negative. The spinal fluid was turbid and under considerable pressure. *The typical budding organism was found in the spinal fluid.* Shortly before death he became deaf, pupil inequality developed and the patellar reflexes disappeared. The autopsy showed *no skin lesions.* There was a diffuse cerebrospinal meningitis and an acute myelitis of the dorsal part of the cord. *No other organs in the body were found to present any marked abnormality.*

CASE III (Hansemann, quoted by Goto[32]).—The man, aged eighteen years, was partially comatose when seen. Examination disclosed a pulse rate of 46, bilateral abducens paralysis, vertical nystagmus, unequal pupils and marked pulmonary tuberculosis. There was vomiting and incontinence of feces and urine. He finally developed delirium and coma, and died in nineteen days. The spinal fluid was at first clear but later became turbid. *The typical organism was found in the spinal fluid, but was at first not recognized as the blastomyces.* The autopsy showed definite and marked pulmonary tuberculosis. The cerebrum and walls of the ventricles were studded with cysts. The same small cysts were found in the meninges. The cysts were small—none larger than a hemp seed. The corpus striatum and part of the optic thalamus were roughened and covered with colloid-like blisters. The pia was infiltrated with lymphocytes and leukocytes. *There were no skin lesions and no other organs were involved.*

CASE IV (Turk, quoted by Goto[32]).—A man, aged forty-three years, epileptic since childhood, and operated on for swelling and suppuration of the cervical lymph glands at the age of eleven years, was suddenly seized with severe headache, vomiting and signs of meningitis. There was marked neck rigidity, a positive Kernig sign, but no involvement of the cranial nerves. The spinal fluid was at first only slightly turbid and under moderate pressure; later the turbidity became more marked and the pressure very high. *The organisms were found in the spinal fluid.* Blood and urine cultures were negative. The autopsy showed definite tuberculosis of the lungs and lymph glands. There was a low-grade meningitis which could not be demonstrated as tuberculous, but in which the blastomycetes were found. There was no tubercle formation. A pathological condition of the mouth, pharynx and esophagus was found. In the pharynx the blastomycetes, mixed with fibrinous exudate, were found deep in the musculature. Turk expresses the belief that this pharyngeal focus was primary and that the organisms reached the meninges from here by way of the blood stream. *No lesions of the skin or other organs are mentioned.*

CASE V (Goto[32]).—The man, aged sixty-one years, had been feeling somewhat ill and irritable for a short time. He complained of a stubborn coryza which would not yield to treatment. Anosmia and deafness in the right ear were noticed soon afterward. The chief complaint was pain in the right occipital region, which became so severe that it interfered with sleep. Ptosis of the right eyelid and diplopia soon appeared. The headache gradually became worse, and he finally developed nausea, vomiting and dizziness. Urine examination revealed glycosuria. Physical examination disclosed right abducens and right hypoglossal paralysis, with atrophy of the right half of the tongue. The reflexes were equal and active. *The lungs were clinically negative.* The eye-grounds were normal. Spinal fluid was at first clear, but developed a fine flocculent precipitate on standing. It contained no globulin. The spinal fluid later became turbid and under increased pressure. *A culture of the first fluid obtained gave one colony of the double-contoured refractile organism, and simple microscopical examination of subsequent specimens revealed the blastomycetes.* The patient gradually became more somnolent, but the headache was still severe. Both knee jerks and the right ankle reflex finally disappeared. At autopsy the dura was normal. Pia and arachnoid contained numerous small submiliary tubercles. These same small tubercles were found on the choroidal plexus. A complete autopsy was not performed. *No skin lesions are mentioned.*

CASE VI (writer's case).—The man, aged forty-one years, with past history negative, has always been healthy. His habits and living conditions were good.

History of Present Illness. He was first taken sick about two and a half months ago with a "cold in the head;" this was not severe and was unaccompanied by any pulmonary symptoms or cough. During this period he developed earache on the left side which continued until the ear began discharging. After about ten days' treatment the discharge ceased. About this time he began having left-sided headache, most intense over the parieto-temporal area and extending back to the occiput. This headache was very intense, but in spite of it he continued to work for about one month, but was finally forced to give up and go to bed. After resting for about one week he felt better and returned to work. The headache became more intense, and after about two weeks he entered the Deaconess Hospital of East St. Louis, Ill. At the time of entry into the hospital there was no clinical evidence of mastoid involvement. Vertigo did not accompany the headache. Several stereoscopical roentgenograms of the head revealed two constant findings: (1) A diffuse haziness of the left mastoid cells, and (2) a fairly well-defined shadow on the left side, beginning near the mastoid area and extending upward and forward, ending near the sella turcica. Examination of the eye-grounds showed the vessels somewhat engorged but otherwise negative. The left tympanic membrane was somewhat thickened and discolored. On March 17 a mastoidectomy was performed by Dr. W. Boyne. His report states that only a minute amount of pus was found in the antrum, but that the mucosa was thickened and edematous.

The *laboratory findings* were as follows: The Wassermann (blood) was negative in both alcoholic and cholesterinized antigens. Several leukocyte counts averaged about 11,500. Differential count: Neutrophiles, 80 per cent; small lymphocytes, 14 per cent; large lymphocytes, 3 per cent; eosinophiles, 2 per cent; basophiles, 0. Before the mastoidectomy the temperature had fluctuated between normal and 100.5° F.

On March 20 the patient was seen in consultation by the writer. Examination showed a well-nourished man, conscious and rational, complaining of severe headache on the left side. *There were no cutaneous lesions.* There was no cough. The pupils were equal; they reacted to light and accommodation, and there was no nystagmus. The tongue protruded in the midline and there were no speech disturbances. There was no neck rigidity. The lungs and heart were clinically negative; the pulse rate was 76. All reflexes of the upper and lower extremities were active and equal. Pathological toe signs were absent; there was no knee or ankle clonus, while Kernig's sign was doubtful. Gross sensory examination was negative. Spinal puncture gave fluid that was water-clear and apparently under normal pressure, with a very faint trace of globulin, and 14 to 18 cells per 1 c.mm. A Wassermann was not done. No organisms were seen.

In view of the history and clinical findings, the most probable explanation was that we were dealing with a brain abscess following otitis media. On March 23 an exploratory craniotomy over the left parietal area was performed by Dr. C. F. Wilhelmj. The brain and meninges appeared normal. Cautious exploratory puncture failed to reveal an abscess cavity. The patient's condition gradually became worse, and death occurred on March 25.

At *autopsy* permission was obtained to examine only the head. The dura was normal, except for congestion and edema around the operative site. Pia and arachnoid over the vertex were congested and edematous, especially on the left side (site of operation). On the base, especially around the optic chiasm, anterior perforated

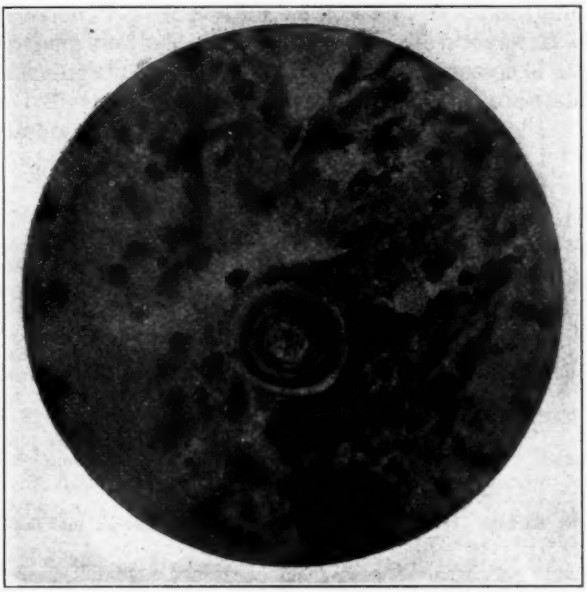

FIG. 1.—A single organism as seen under high magnification.

space, and over the pons, the pia and arachnoid were studded with numerous very minute tubercles of a grayish-yellow color. There was no exudate. Sections through the brain failed to reveal any abscess formation. From these findings a macroscopical diagnosis of tuberculous meningitis was made.

Microscopical examination of the pia and arachnoid from the base of the brain showed round-cell infiltration, collections of giant cells and numerous double-contoured budding yeast-like organisms, which showed no evidence of endosporulation (Figs. 1 and 2).

The portal of entry of the infection in this case is uncertain; most likely it occurred through the upper respiratory tract during

the initial period of coryza, but the possibility of a blastomycotic infection of the middle ear cannot be definitely excluded, since no cultures or microscopical examinations were made from the discharge.

An analysis of these 6 cases yields the following interesting and important data which differentiate them clinically from the usual case of systemic blastomycosis, with or without meningeal implication: (1) *Skin lesions were absent in all cases;* (2) bone or joint involvement, so common in ordinary generalized blastomycosis, was not present in a single case; (3) necrosis and destruction of the skull bones, apparently an important etiological channel for meningeal infection in systemic blastomycosis, was not a factor in these

FIG. 2.—Low magnification, showing two organisms.

cases; (4) the organism was found in the spinal fluid of 4 cases; (5) complete autopsies were performed in 4 cases (in 2 of these no mention is made of blastomycotic lesions in any other organs, the lungs were involved in 1 and the mouth, pharynx and esophagus in the fourth); (6) the 2 incompletely autopsied cases gave no clinical evidence of pulmonary or other organic invasion.

Conclusions. While the 6 cases of blastomycotic meningitis analyzed in this paper are in many respects very different from the usual case of systemic blastomycosis, it is doubtful whether or not these differences are of a fundamental nature. There is no substantial evidence to show that the portal of entry, the causative

organism, or other etiological factors, belong to a separate category. The divergence of the clinical course and pathology is no doubt due to the fact that when the meninges are infected during the initial period of invasion, death usually occurs before the typical, extensive, metastatic foci become established. In an etiological sense, therefore, this group probably does not deserve separate classification. Practical clinical classifications, however, should be devised with a view toward their utility in diagnosis, their scientific accuracy being superseded only by this aim. From this viewpoint we are fully justified in recognizing a *primary meningeal form* of systemic blastomycosis which may occur without gross clinical evidence of systemic invasion.

In conclusion, I wish to thank Dr. C. F. Wilhelmj and Dr. W. Boyne for their kind permission to publish the above case of blastomycotic meningitis, and Dr. D. H. Dolley, Professor of Pathology, St. Louis University Medical School, to whom I am indebted for the microscopical diagnosis.

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PRIMARY INOCULATION TUBERCULOSIS OF THE SKIN WITH METASTASIS TO REGIONAL LYMPH NODES.*

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During the last eight years, 10 cases of undoubted, and 2 of probable, inoculation tuberculosis of the skin were observed in the Section on Dermatology and Syphilology of the Mayo Clinic. This group constitutes a definite but unfamiliar type of the disease. A better acquaintance with the clinical characteristics of this lesion would result in the identification of more cases, especially by those who, as surgeons, internists, pediatricians, and roentgenologists, are required to deal with superficial tuberculous adenopathies. The demonstration of illustrative cases from this series before the staff of the Mayo Clinic has resulted in the identification of new cases, several of them among physicians and veterinarians.

Inoculation tuberculosis of the skin is known to most physicians as the so-called postmortem wart or verruca necrogenica, a local lesion in the skin usually interpreted as the reaction of a resistant person to inoculation with the bacillus of tuberculosis; in other words, a superinfection. The animal homologue, in which the infected guinea-pig becomes immune to glandular metastatic tuberculosis following inoculation with the bacillus of tuberculosis, even though a local lesion develops, on reinoculation is familiar to experimental workers with this disease. Tuberculosis verrucosa cutis should then, theoretically at least, be the typical reaction of the previously-infected adult to a cutaneous inoculation; and involvement of adjacent lymphatic structures, or systemic infection, should be and is, rare from this type of lesion. Inoculation tuberculosis of the skin, with extension to lymph nodes, and systemic infection should, in theory, be possible only in infancy or early childhood, before systemic infection has developed resistance.

That this immunological rule cannot be applied too strictly to the human problem of inoculation tuberculosis, has been evidenced by the gradual accumulation in the literature of a group of reports describing primary tuberculous inoculation and lymphatic metastasis, in some cases with generalization of the infection, in adults who could scarcely have escaped previous tuberculous infection. Naturally enough, most of the reported cases of this type of tuberculosis are in infants and children. But the demonstration of a group of cases in supposedly resistant adults indicates that the problem of immunity to tuberculosis is, like that of resistance to

* From the Section on Dermatology and Syphilology, Mayo Clinic. Read before the College of Physicians, Philadelphia, October 27, 1924.

syphilis, not to be summed up by presupposing a resistant or susceptible host and a standard organism, but involves, as Jadassohn[15] well expressed it, the consideration of an almost infinite range of interplay between the susceptibilities of the host and the virulence or avirulence of strains of infecting bacilli of tuberculosis. The complexity of the problem is exemplified by the variety in the results of subcutaneous inoculation, in that in one case it may result in an indolent inflammatory lesion like the verruca necrogenica, in another in the formation of a few tubercles in the fat at the inoculation site and a rapidly developing tuberculous adenopathy, while in a third, there may be a violent inflammatory reaction at the point of entry, which destroys all traces of the organisms but does not occur in time to prevent lymphangitis and adenitis beyond the lesion.

Clinically, tuberculosis verrucosa cutis and primary inoculation tuberculosis of the type described can be quite sharply differentiated. The verrucous form consists of a warty, horny inflammatory papule with villi studding the surface. On pressure small amounts of pus can sometimes be made to exude between the villi. There is little deep infiltration, most of the activity being confined to the upper corium in association with the verrucous changes in the epidermis. In the primary inoculation tuberculosis discussed here, there is no verrucous hypertrophy. The essential lesion is a tubercle rather deeper than that in the verrucous form, better defined and less involved in general tissue reaction. The lesion, clinically, is usually flat, and consists of a group of miliary nodules around a central slightly depressed scar or superficial ulcer. In a few cases there may be deep induration and slight swelling, but as a rule even these are absent. It is the inconspicuousness of the primary inoculation that so often permits it to escape attention in the more active consideration of its consequence.

The Literature. The report by Tscherning[24] before the first session of the Congress for the study of tuberculosis at Paris in 1888 furnishes one of the early examples of this type of tuberculous infection. A servant, attending a tuberculous master, wounded a finger with a fragment of sputum cup. Lymphatic involvement followed and it was necessary to amputate the finger and remove the affected glands before recovery ensued. Bacilli of tuberculosis were demonstrated in the tendon sheath. Lennander,[17] in 1889, reported on a tuberculous inoculation apparently following smallpox vaccination in early childhood. Hartzell[12] in 1898, reported 3 unusual examples of inoculation tuberculosis of the hand and fingers, but the lesions were apparently of the verrucous type. Jadassohn,[15] in his authoritative and complete review of tuberculosis of the skin in the Mracek Handbuch (1907), mentioned in brief descriptive terms the types of inoculation tuberculosis of the skin designated as tuberculous chancre and epithelioma-like tuberculous indurated ulcers; but the picture of primary inoculation as

here described was evidently not then clear-cut even to an author of such large experience. In 1909 Escherich[9] reported an inoculation tuberculosis of the cheek in a child, as part of his consideration of inoculation portals for the disease in nurslings. Epstein[8] (1912) described 2 cases of inoculation tuberculosis of the ear in children following puncture for ear-rings. These 2 were characterized by fulminating local reaction and the destruction of the lobule of the ear, but no generalization of the process. In 1913, Holt[14] reported a case of tuberculosis of the foreskin and penis, with fatal outcome from tuberculous meningitis, following ritual circumcision. His summary of the earlier literature of this form of inoculation tuberculosis, included an instance in which one person had been responsible for the infection of 10 children. Of the 41 patients considered, 16 had died and 13 recovered, the remainder having been lost sight of. The local tuberculous reaction appeared within a week, lymphatic involvement within two or three weeks, and systemic generalized infection, if it occurred, about the third or fourth month. The best results followed the removal of affected lymph nodes. Most of the cases were regarded as syphilitic infections at the outset.

A wave of reports and references to the literature appeared between 1910 and 1914. Brault,[3] Curschmann,[5] Hamburger,[11] and Boeck[2] cited cases of vulvar tuberculosis in children, with inguinal adenitis, resulting from playing on infected floors; Baumel[1] reported cases of tuberculosis inoculated on eczematous lesions. An inoculation on the forehead of an eight-weeks' old child was reported by Scheltema,[23] and the case of a child of fifteen months who developed primary tuberculosis on the thumb, with a large axillary bubo, was was reported by Boeck. Chancellor[4] described 2 excellent cases of primary inoculation tuberculosis, 1 of them from the practice of the late John B. Murphy. In 1 case the primary lesion on the cheek which was followed by lymphatic metastasis, was directly traced to the playful bite of a nurse. On examination her sputum was found to teem with bacilli of tuberculosis. In the other instance, a child's cheek was infected by a scratch from a pin which had been carried between the lips of a tuberculous uncle who often fondled and kissed the child. Lipschütz,[18] in 1914, discussed the possibility that local tuberculous inoculation of the skin might be traced not infrequently to avian bacilli, and emphasized the large number of organisms to be found in such lesions. In 1914 Romer[22] stated that the study of the question of tuberculous infection through the skin was still in its beginning and that its frequency could not, therefore, be estimated.

In 1921, following the hiatus of the war, Ravenel[21] described 3 examples of inoculation tuberculosis, in 1 of which the accidental incision, after being cleansed with mercury bichlorid, healed and did not break down for three weeks. None of these cases, however, seems to have been accompanied by lymphatic metas-

tasis. In the same year Davis[6] reported a case of inoculation tuberculosis following cat-bite. Dietl[7] described an excellent case, in which a sixteen-months' old child, whose mother had tuberculosis, was brought to the hospital for examination as a precautionary measure, The child was normal and the von Pirquet and three subcutaneous tests were all negative. Two months later the child was again brought to the hospital with impetigo of the feet and an ulcer 1.5 by 2 cm. on the back. A mass of enlarged lymph nodes had appeared in the left axilla following the development of the ulcer. On excision the lesion was found to be tuberculous. The von Pirquet test was now positive, but there was no other evidence of systemic tuberculosis. In 1922, Lutz[19] presented an excellent summary of tuberculosis of the skin, with a degree of attention to primary cutaneous inoculation that indicates the growing appreciation of the interest and importance of this variety. Hochstetter,[13] in 1923, reported an example of verrucous tuberculosis on the wrist with what he believed might have been evidence of generalization in the form of tuberculous epididymitis. Joyce,[16] in 1923, described 2 clear-cut cases, of a mother inoculated on the chin and her child on the cheek, presumably by the tuberculous father. The most recent report is that of Nixon and Short[20] (1923) in which 4 cases of so-called tuberculous chancre were described. The first was that of a mother who sustained inoculation on the chin with formation of a papule and development of a submental adenopathy, apparently from the kiss of her tuberculous son. The second was a child aged six years who, following a cut over the patella which did not heal for six months, developed an enlarged lymph node in the groin. Tuberculosis was demonstrated in both lesions and uneventful healing followed excision of ulcer and node. The third patient, a child of thirteen years, developed an inflammatory reaction of the eye and a hard nodule at the outer canthus following a blow on the cheek. What seemed to be miliary tubercles appeared along the palpebral conjunctiva, and the nodule broke down. On excision it was found to be tuberculous, and recovery followed. The fourth case is of especial interest because the nodule on the upper lip, which followed a bruise on a small vesicle at that point, after rapidly enlarging, responded promptly to neoarsphenamin administered on the supposition that the lesion was a syphilitic chancre. On excision it was found to be tuberculous.

Efforts to ascertain the frequency of primary inoculation tuberculosis of the skin have resulted only in the finding of a quotation by Epstein from a report by Ghon,[10] of 2 cases of caseous tuberculosis of the preauricular nodes in 184 necropsies on children. In these cases there seem to have been signs suggestive of a cutaneous portal of inoculation.

It will be apparent from even this partial review of the literature that the picture of primary inoculation tuberculosis of the skin

(excluding tuberculosis verrucosa cutis) has been gradually taking form over a period of years, and that a type with varying, and sometimes slight, degrees of local reaction but important extension to adjacent lymph nodes, is assuming distinct definition. In order the more clearly to delineate the type and to illustrate some of the diagnostic problems involved, condensed reports of 10 cases are presented.

Reports of Cases. Three types were recognized: Inoculation on the face, illustrated by 5 cases; inoculation on the forearm or hand, illustrated by 3 cases; and inoculation on the foot, illustrated by 2 cases. Two patients had what seemed to be tuberculous lesions of the umbilicus, whose right to be called an inoculation focus is as yet undetermined. In contrast to the tenor of the literature, only 3 of the patients were young children, two, four and five years of age. Three were adolescents, thirteen, sixteen and seventeen years. Four were adults, all of them over thirty, and 2 nearly or over forty years. There were 5 males and 5 females. Most of the patients were in the best of health at the time of infection, to all outward appearances, only 1 child being sickly following measles. The relatively benign character of the infection was apparent from the continued good health of the patients, the absence of signs of generalization of the infection, and the good response of the majority once a technic of treatment had been developed. Complete studies were not made on the earliest case, because it was not promptly diagnosed. But taking the group as a whole, the tuberculous nature of the condition was carefully checked by clinical and laboratory tests, including animal inoculations, and exclusion of syphilis. Sporotrichosis and actinomycosis were later excluded by cultural and microscopical methods, respectively.

Case I.—A boy, aged two years, seen in 1917, presented a massive swelling with a number of discharging sinuses over the right preauricular and cervical regions (Fig. 1) and temperature of 101.4° F. The first involvement had appeared above the parotid gland five months previously, and had progressed downward, with successive incisions for drainage. Above the right malar prominence was a small depressed scar-like lesion, about 1 cm. in diameter, around which a few apple-jelly nodules could be demonstrated by diascopic pressure. No information as to the origin or course of this lesion was obtainable. Bacilli of tuberculosis were present in the caseous material and discharge from the lymph nodes. Tonsils and adenoids were enlarged, but except for slight bronchial thickening, the lungs were clear. The child's general health had remained good. The examination of the mother was incomplete, but it was noted that roentgen-ray examination of her chest showed tuberculosis of both apices. Following tonsillectomy, adenoidectomy, and

partial excision of the cervical nodes, with coincident administration of six intravenous injections of neoarsphenamin for its non-specific effect, rapid improvement followed. Ten months later the child was gaining steadily, and roentgen-ray treatment of the nodes was advised.

Although the cart was placed before the horse in the diagnosis of this case, the lesion on the temple being regarded as auto-inoculative or mestastatic, and the correction only made in retrospect, all the essentials for a presumptive diagnosis of primary inoculation tuberculosis, except the time sequence, were present. Attention should be particularly drawn to the primary lesion, a small scar-like depression with the so-called apple-jelly nodules in the faintly pink areola of slightly-inflamed tissue around the scar. A few such nodules persisted in the scar itself.

The apple-jelly nodule, on whose identification at the site of inoculation the clinical diagnosis will often depend, is a tubercle in the deeper layers of the corium or in the fat, which though ordinarily invisible in the pink or red of the inflammatory base, can be detected by expressing the blood from the tissue with a glass spatula, the lip of a tumbler, or even a microscopical slide. When viewed thus, the brownish translucent miliary tubercule, 1 or 2 mm. in diameter, stands out clearly against the pale background. Apple-jelly nodules, so-called on account of their color, are not absolutely characteristic of cutaneous tuberculosis, for coarse ones may be found in certain tuberous and nodose hypertrophic syphilids. In general, however, they are a helpful guide to diagnosis, and often the first feature to arouse suspicion at a site of traumatic inoculation. In Case I, the successive involvement of parotid, cervical and submental glands suggests the usual course of lymphatic metastasis from a cutaneous lesion.

CASE II.—A girl, aged seventeen years, seen in 1917, complained of an ulcer on the left cheek of six-months' duration (Fig. 2). On examination it was found to be partially healed, forming a plaque over the left zygoma whose center was covered with epithelium and whose periphery was marked by scattered apple-jelly tubercles. Just anterior to the left ear was a subcutaneous bluish infiltration, and just below this the anterior auricular lymph node had broken down. The node had been drained, but no stain had been made for bacilli of tuberculosis. Although the patient was pale and the right apex showed slightly increased fremitus, the general examination gave no evidence of systemic infection. Three hundred milligram-hours of radium and a curettage of the lymph node failed to afford relief. The primary lesion was excised as epithelioma, after her departure, according to a letter received.

The study of this case must be regarded as incomplete, but its clinical details accord with subsequent observations of other cases.

CASE III.—This was the first example of inoculation on the foot in the series and although primary lesion and metastasis were far apart and not visibly connected, it was possible satisfactorily to relate the two by clinical and laboratory evidence. A boy, aged five years, seen in 1919, had developed a mass in Scarpa's triangle, following a fall. In order to indicate how completely the history of a case may mislead an examiner, the following literal transcript is made: "This child has always been strong and robust. Two months ago he was supposed to have injured the inner side of the thigh riding a tricycle. After a few weeks a lump appeared at the point of injury, tender but not inflamed. It gradually enlarged. After a poultice had been applied for some time the lump softened and opened up with slight discharge. The child was now operated on, a growth the size of a hen's egg being removed, and reported to be a lymphosarcoma. It has always been noted that scratches and abrasions heal slowly." No note was made of any other injury than the fall. The operative wound failed to heal and a chronic ulcer formed. A search for a primary lesion, following a report of inflammatory tissue in a section from the ulcer, revealed the inoculation focus on the great toe. Thereupon, further questioning of the mother recalled the fact that the boy had had a small infected lesion at this site which was opened and drained two or three weeks before the trouble in the groin, and subsequent to the fall from the tricycle. The primary tuberculous lesion thus identified consisted of a group of apple-jelly nodules, with only the slightest surrounding inflammatory reaction, around a healed cut on the inner side of the left great toe. A section including several apple-jelly nodules was then taken from the inoculation site and typical tubercles demonstrated histologically. Radium to the toe and the lymph nodes resulted in rapid healing and the boy was reported in good health six months later. The von Pirquet test was strongly positive at the time the diagnosis was made, but no other evidence of systemic tuberculosis was found.

CASE IV.—This was the third instance of inoculation on the face, and presented several puzzling features. A boy, aged four years had run a stick into his left tonsil ten months before examination (1920). Two or three days later the mother noticed a small lump under the skin of the sternocleidomastoid region. Coincidently a small pustule on the left cheek about 5 cm. above the angle of the mouth was noticed. The lump on the neck increased in size, softened was opened, healed and broke down again three weeks after an attack of measles. Since the measles the child had been sickly, with occasional fever and vomiting, and had suffered what was regarded as an attack of unilateral "mumps." This apparently consisted of a marked rapid enlargement of the lymph nodes on the left side of the neck with profuse discharge from a sinus. There was no

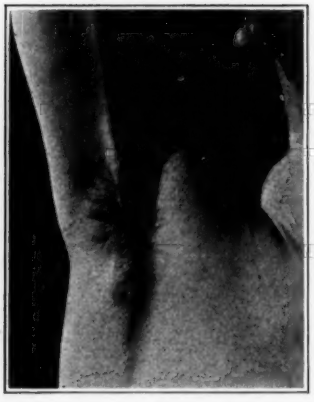
FIG. 1

FIG. 2

FIG. 1.—Probable primary inoculation site on right temple (Case I) with metastatic tuberculous lymph nodes.

FIG. 2.—Primary inoculation tuberculosis (upper lesion) with typical broken down metastatic lymph nodes. Note the miliary tubercles in the margin of the tuberculous lesion, and the depressed scar-like center.

FIG. 3.—Tissue from the primary inoculation site on the great toe (Case III). Note the typical tubercles deep in the cutis, which could be seen as apple-jelly nodules under glass pressure.



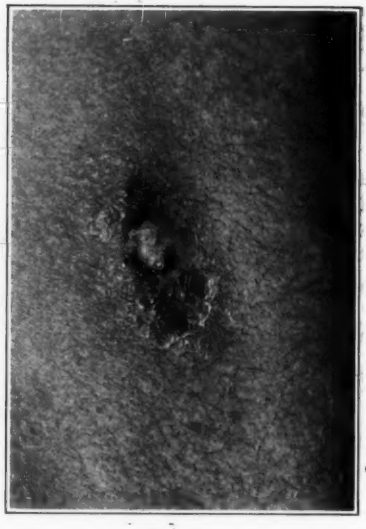


FIG. 4 FIG. 5

FIG. 4.—Tuberculous lymphangitis of the upper brachial lymph channels leading to a softened axillary lymph node. The primary lesion is shown in Fig. 5. The lymphangitis could be recognized only on raising the arm, and was indolent and non-inflammatory (Case V). The same condition developed in Case IX.

FIG. 5.—Primary focus on the forearm, of one year's duration (Case V).

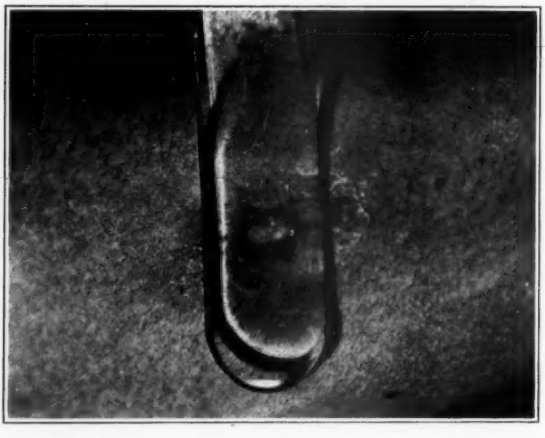


FIG. 6.—Effect of glass pressure in bringing out the barely visible ring of tubercles (apple-jelly nodules) in the scar.

FIG. 8.—Tubercles in the border of the healed scar of a cut on the ball of the toe (Case VI). Metastasis occurred to the lymph nodes in Scarpa's triangle.

FIG. 7.—Note the scar at the site of thetuberculous glands in the left Scarpa's triangle, removed at operation (Case VI). Four months later, after a recurrence, the primary focus was discovered on the left great toe, as indicated by the pointer.

FIG. 9.—Primary inoculation tuberculosis on the cheek of a young girl (Case X). There was a nodule over the ramus of the jaw, and a slightly enlarged node just below the ramus.

FIG. 10.—Effect of four months' treatment of the lesion shown in Fig. 9, using the Kromayer lamp with pressure, general ultraviolet irradiation, and neoarsphenamin intravenously. Diagnosis confirmed histologically, syphilis and sporotrichosis excluded.

FIG. 11.—Sporotrichotic primary inoculation of the upper lip, confirmed culturally and disappearing under iodid. Note the chain of metastasis.

familial or contact history of tuberculosis. The focus on the left cheek consisted of a small dry crateriform scar-like depression midway between the zygoma and the left labial commissure, with typical apple-jelly nodules scattered about the immediate periphery of the lesion. Below the ramus of the left jaw was a sinus leading to an enlarged lymph node. There was little or no discharge, and through oversight neither cultures nor stained smears were made. The von Pirquet test was negative, and the chest, which at first showed some hilus infiltration, was reported normal three months later. No sulphur bodies could be found. The diagnosis of primary inoculation tuberculosis remained clinical therefore, and the patient was treated with radium. Complete healing and no recurrence was reported a year later after the application of 1040 milligram-hours of radium to the neck, and 575 milligram-hours to the primary lesion.

In view of the negative von Pirquet test, which, however, was not repeated, and the incomplete laboratory study, this case may remain *sub judice*, although the morphological appearance of the cutaneous lesion was typical of the series. The tonsillar injury gave the impression of coincidence rather than cause.

CASE V.—This case, seen in 1921, was the first of the series showing infection on the arm, and occurred in a veterinary surgeon, aged thirty-nine years, who sought relief from a draining sinus in a softened node in the right axilla. His discomfort was due as much to the sense of tenseness and difficulty in extending the arm, as to the discharge itself. There was no familial history of tuberculosis or of contacts with human tuberculosis, but the patient was constantly exposed to bovine and avian infection in the course of his operative and postmortem work. The dermatological consultation had been called to consider the advisability of using arsphenamin in preference to surgical excision of the node. On further examination, a pipe-stem indolent lymph angitis was found to explain the discomfort on movement of the arm. The cause of the difficulty did not become visible until the arm was fully extended above the head (Fig. 4). On search for a primary focus a small discolored scar-like patch was found on the extensor surface of the forearm, the remains of a nodule that on its appearance a year before, had been cauterized with phenol and iodin and subsequently disappeared (Fig. 5). In the center of this scar, under glass pressure (Fig. 6), a ring of about a dozen small apple-jelly tubercles, acting as the feeder focus for the lymphangitis and adenitis, was identified. The epitrochlear lymph node was only slightly enlarged. The excised axillary node showed typical tuberculosis with caseation, and the widely excised primary focus on the forearm also showed typical tubercles. A few acid-fast organisms were found in the skin sections. Inoculation of guinea pigs was not successful, the animals

dying from secondary infection. Inoculation of hens and roosters was negative.

The treatment in this case consisted of excision of lymph node and primary lesion, the latter being removed down to the fascia; one course of 5 injections of neoarsphenamin, and 33,356 milligram-hours of radium to the axilla and along the course of the involved lymphatics and the excision scar. Slight edema of the hand developed and disappeared uneventfully. A year after diagnosis the patient developed an ischiorectal abscess which did not appear to be tuberculous and which healed promptly after simple drainage. At no time either on first examination or subsequently, during a three-year period of observation has there been any sign of systemic infection.

CASE VI.—A boy, aged thirteen years, seen in 1921, was the clinical twin of Case III, seen in 1919, This previously healthy youth had developed a mass in the inguinal region which broke down and discharged three weeks after the healing of a cut on the outer aspect of the left great toe. The connection with the injury was more easily traced than in Case III. The toe had been cut by a piece of tin and had healed without complications, but a mass about 5 cm. in diameter had appeared in the groin just three weeks later. This had subsided of itself but had lately recurred. The scar on the toe had likewise shown signs of renewed activity, having opened and drained one month before the patient came to the clinic. A surgical diagnosis of tuberculous adenitis, confirmed by pathological examination and positive guinea-pig inoculation from the excised lymph nodes in Scarpa's triangle, was made, but the primary lesion on the toe was overlooked. There was a recurrence of the adenitis four months later, this time in the inguinal region, and dermatological consultation was then called to consider arsphenamin as adjunct treatment. The primary focus on the great toe (Figs. 7 and 8) was then found and the presence of apple-jelly tubercles demonstrated in the healed scar by glass pressure and in the excised tissue following biopsy. Guinea-pig, rabbit and chicken inoculations from the toe were negative. Microscopical examination of the skin from the focus showed the tubercles to extend much more deeply into the fat than the biopsy excision, so that an almost complete dissection of the soft tissues of the ball of the toe was then necessary, though it delayed healing somewhat. Large doses of radium, two roentgen-ray exposures, and a course of 8 injections of arsphenamin were employed, with apparently complete recovery during a two-year period of observation. The only ascertainable connection with a source of tuberculous infection was a sister who had had Pott's disease, but who had been away from home for some time.

This case, like others later, furnishes an excellent example of the continued vicious activity of the "feeder focus" and of the benefit

derived from its removal with the recognition of the lymphatic metastasis.

CASE VII.—This case was diagnosed by the Medical Division of the Clinic following the demonstration of Cases V and VI before the staff. A woman, aged thirty-four years, who had a carcinoma of the cervix diagnosed and operated on in 1920, returned in 1922 with a recurrence and inoperable metastatic lesions. In the course of her examination a chronic lymphangitis of the left arm was recognized. The presumptive primary site was found on the palmar surface of the left hand, where she had had a sore a year before. The epitrochlear node had been involved, and had been incised with prompt healing. The axillary lymph nodes had likewise enlarged and discharged, but were now healing spontaneously. Numerous apple-jelly nodules were, however, demonstrable in the incision scar. The scar of the primary inoculation site contained no tubercles demonstrable by glass pressure, but a biopsy from the epitrochlear scar revealed many, some of them deep in the subcutaneous fat. The patient's condition was so serious as a result of the carcinoma that no further study or treatment was attempted.

It is striking here, as in other cases of this series, and in the literature, that the presence of tuberculous infection was no bar to the healing of the inoculation lesion, the reaction of the subcutaneous tissue being trivial, while that of the lymphatic tissue was much more pronounced.

CASE VIII.—The case of a woman, aged thirty-eight years, seen in 1923, illustrates the years of activity during which a feeder focus may be responsible for a persistent lymphatic involvement, and the relative ineffectiveness of roentgen ray, at least, in the treatment of such primary inoculation sites. The chief complaint was enlargement of lymph nodes on the right side of the neck and beneath the chin, of three years' duration. The onset was marked by the abrupt enlargement and softening of a single node, and subsequent involvement of others, with successive incisions for drainage but without real improvement. A small reddened patch on the right cheek, present for five years, and antedating the lymph node involvement by two years, had been regarded as "lupus" and ignored until recently, when in the belief that it was an epithelioma, roentgen-ray treatment and a small amount of radium had been administered to the point of cutaneous reaction, with the production of atrophy and telangiectasia. The tonsils had been removed two years before the appearance of the adenitis. Pus from the nodes was negative culturally and showed no bacilli of tuberculosis on staining. Under glass pressure, the scar-like "lupus" patch presented little that could be called apple-jelly nodules, so that it was

with some hesitation that its removal with the nodes for diagnosis was advised. It was surprising to find that this supposedly "cured" focus contained, in spite of radiotherapy carried to the point of cutaneous reaction, large numbers of typical tubercles and giant cells, apparently in full activity. The systemic examination revealed no other evidence of tuberculosis, and no good history of contacts could be obtained. The patient did not remain for systemic treatment, but reported subsequently that enlarged lymph nodes had begun to appear under the other side of the chin. It is worth repeating that this lesion (see also Case II) had been treated with roentgen-ray as epithelioma, and not as tuberculosis.

CASE IX.—This patient, a physician in middle life, presented himself with the statement that he had made his own diagnosis on the basis of Case V in this series, which he had watched from the time the diagnosis was made. On examination he presented the same type of pipe-stem lymphangitis in the upper brachial region, visible only on extending the arm above the head (Fig. 4.) An axillary lymph node had softened and in the draining pus, numerous bacilli of tuberculosis had been demonstrated. The primary inoculation focus had been situated on the extensor surface of the forearm, apparently, and had been furuncular in character. Healing had been complete, and although the scar was subsequently completely and deeply excised and serially sectioned no tubercles and only the densest scar tissue could be found. There was no systemic evidence of tuberculosis elsewhere. The lymph nodes were not excised but radium was liberally used, and neoarsphenamin administered, with apparently good results.

This sharp reaction with complete scarring and destruction of all organisms at the inoculation site, although not verified by animal inoculation, is apparently what occurred in Case VII. This is theoretically possible, as is found in the tuberculids if the host is sufficiently resistant to destroy all organisms at the point of entry in a furuncular reaction, even though some of them escape to cause trouble in the lymphatic system. Subsequent inoculation of an exposed, healing "boil" seems less likely in view of the absence of tubercles in the scar.

CASE X.—This patient, a healthy girl, aged sixteen years, presented some of the therapeutic problems of this form of tuberculosis of the skin. The inoculation lesion developed on the cheek; the patient thought she had infected a pimple by scratching it. At the time of examination the lesion was an induration with an ulcerative surface and a few scattered puncta, midway between the zygoma and the right labial commissure (Fig. 9). A small bluish nodule over the jaw, and an enlarged lymph node beneath the ramus were

due to metastasis. No history pointing to a source of infection could be obtained, although the patient lived on a farm. Sporotrichosis and extragenital syphilis were carefully eliminated, and a biopsy showed the presence of tubercles in the lesion. The extensive induration (2 cm. in diameter) with the metastatic lesions, would, if treated surgically, involve a gross disfigurement of the face. It was accordingly decided to try the Kromayer lamp with pressure, and to use ultraviolet light (Alpine sun) and arsphenamin conjointly, as systemic treatment. The response was gradual but ultimately very satisfactory. The lesion healed completely (Fig. 10) under repeated severe reactions in the course of four months. The induration disappeared, and the metastatic lesions subsided. Observation of the case terminated before the ultimate result could be determined.

Two cases have also been observed in which the diagnosis of inoculation tuberculosis is not yet proved, although laboratory evidence suggests the tuberculous character of the initial lesion. Both lesions developed at the margin of the umbilicus. In the one which was observed from the start, the patient's first complaint was of pain across the abdomen. An indolent furuncle-like lesion pointed at the upper margin of the umbilicus and discharged, leaving a draining sinus whose appearance suggested a tuberculous origin. Smears from the pus showed acid-fast organisms. Guinea-pig inoculations resulted in varying opinions and an indefinite conclusion, but the lesions simulated tuberculous infection with involvement of lymph nodes and viscera. The general examination of the patient was entirely negative and no signs of a visceral focus could be found. A solitary enlarged node appeared in the right axilla. There was no lymphangitis and the node did not soften. Radium to the umbilicus and the axillary and inguinal lymph nodes, with neoarsphenamin and a general regimen for tuberculosis resulted in a prompt disappearance of symptoms which had, in fact, begun to disappear before the treatment was started. There has been no sign of relapse. A second case had a similar history, but a draining sinus persisted for several months after the initial lesion. There was some disagreement as to the identity of the acid-fast organisms found in the first case, and the tuberculous character of the reactions in animals was again open to question in the first case. These cases, therefore, must be thought of as still *sub judice*.

The importance of differentiating lesions of this type from sporotrichosis, will be apparent to all who are clinically familiar with the two conditions. Fig. 11 illustrates a sporotrichosis of the lip, conforming in every particular to the clinical picture of inoculation tuberculosis except that typical apple-jelly nodules were not recognized. The condition was culturally identified as sporotrichosis. The response of tuberculous and occasionally sporotrichotic lesions

to arsphenamin treatment obscures the differentiation from syphilis, and warns against relying implicity on therapeutic tests with this drug. This is especially important in cases occurring about the genitalia, as noted by Holt[14] and by Nixon and Short.[20] The complete substantiation of a diagnosis of primary inoculation tuberculosis should include the finding of apple-jelly tubercles in the gross lesion, bacilli of tuberculosis in the smear, a negative culture for sporothrix, absence of actinomyces in the pus, positive guinea-pig inoculations of pus and tissue from both primary and secondary lesions, and the demonstration of tubercles in excised tissue from the focus and the lymph nodes. In practice it is difficult to make this chain of evidence complete, but the finding of a focus and presumptive extension to the lymphatic drainage area, with apple-jelly nodules in the primary focus and the histological demonstration of tubercles in excised tissue from both primary and secondary lesions, in the absence of other systemic forms of tuberculosis, makes the diagnosis of primary inoculation tuberculosis reasonably sound.

Summary. The literature is summarized and 10 cases described, of inoculation tuberculosis of the skin with extension to lymph nodes. These cases are equally distributed between the two sexes and in childhood, adolescence and adult life. They suggest that reaction to tuberculous infection and its sequelæ varies with the individual and with circumstances, rather than entirely with previous infection and acquired resistance.

The lesions described as primary are often inconspicuous, may be far from the site of metastatic lymphatic lesions, and are often in old traumatic scars. A history of exposure to tuberculosis may not be obtainable. The apple-jelly nodule, or tubercle in the cutis and subcutaneous fat, is the elementary essential lesion. Its identification by diascopic pressure is the first aid to a diagnosis.

The primary lesion may be confused with syphilitic chancre, sporotrichosis, actinomycosis and epithelioma; the lymphatic metastatic lesions with lymphosarcoma and simple inflammatory bubo.

A painless and indolent lymphangitis may be the only symptom attracting attention in cases primary on the arm, and this may only become visible on the fullest extension of the arm above the head.

A delayed adenopathy, developing after even trifling trauma, should lead to examination of the lymphatic drainage area for a tuberculous inoculation focus.

A primary focus may serve throughout a period of months or years as a feeder to a lymphatic lesion, and be responsible for repeated recurrence of adenitis in spite of drainage, curettage and excision. Scrofulodermatous ulceration of the skin may result at the site of the metastatic lesion.

Roentgen-ray carried to the point of reaction may not destroy the primary focus or retard its feeder activities.

Excision of the primary focus, even if it is only a scar, and of its secondary lymph nodes, is necessary to the best treatment, and should be carried out whenever possible.

In dealing with the focus it is usual to find that the tubercles extend much deeper than might be anticipated, and excision should therefore be carried to the fascia and widely marginated.

Radium controls the lymphatic metastatic lesion and is preferable to the roentgen-ray after excision, in the treatment of the excision scars and drainage areas. Large doses, properly screened, should be used, but not carried to excess.

Ultraviolet light from the quartz lamp can be used locally with pressure, in lesions that cannot be excised, and should be employed systemically in the form of general irradiation and artificial heliotherapy.

Moderate doses of neoarsphenamin, which contribute to a good result in cases of tuberculids, and in some cases of tuberculous adenitis, may be used in the treatment of primary inoculation tuberculosis, as part of the general management of the case.

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FURTHER OBSERVATIONS ON THE EPIDEMIOLOGY OF PEMPHIGUS NEONATORUM.

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In a recent paper[1] we have directed attention to the possibility that the mother's milk may be a source of infection for infants suffering from the condition known as pemphigus neonatorum or impetigo, as it is sometimes called. We wish to state emphatically that it is not our opinion that these observations have solved the problem of the control of the epidemic form of this disease in institutions; neither would we take the position that the work done so far constitutes final proof that the milk actually *is* a source of infection for the infant.

However, we do take the position that inasmuch as the Staphylococcus aureus is at present regarded as the cause of pemphigus neonatorum, the very frequency with which normal milk contains these organisms makes it conceivable that certain strains of them may be virulent and thus assume etiologic importance. Moreover, when all sanitary precautions are aimed to prevent these cocci from reaching the infant, why disregard a source that may yield more of them than is likely to come from all others combined? We trust that this conservative statement of our position will finally counteract the garbled misrepresentation to which the lay press has subjected us.

One of the obstacles that renders conclusions impossible at present has to do with the fact that Staphylococcus aureus may be present not only in the normal milk of women whose infants develop pemphigus but often in the milk of those whose infants do not develop it. However, this fact in no way rules out the

possibility we are considering, the great variation in virulence of these organisms being well recognized. The situation is comparable to that existing with suppurative mastitis. Dudgeon and Jewesbury[2] find that Staphylococcus aureus is the most important organism in this condition, yet suppurative mastitis is infrequent in comparison with the number of milks containing Staphylococcus aureus.

As regards the presence of Staphylococcus aureus in normal milk, the literature as well as our own experience shows the greatest irregularity. Dudgeon and Jewesbury[2] quote Köstlin,[3] who found Staphylococcus aureus in 23 per cent of 100 pregnant women, where the so-called albus variety was present in all cases. In 14 cases the secretion was sterile. During the puerperium Staphylococcus albus was present in 132 and Staphylococcus aureus in 79 and "bacilli" in 22 from 137 cases studied. On the other hand, Cohn and Neumann[4] isolated Staphylococcus aureus only once from the milk of 48 women. This astonishing variation is comparable with our findings at different times. For example, as we reported in the previous paper, from the limited number of controls made from mothers whose babes did not have pemphigus, pigmented cocci were not isolated from any of the cases examined (approximately a dozen); yet more recently during a period of prolonged freedom from the disease, culture of 25 cases showed an incidence of about 30 per cent of aureus in one or both breasts. However, in about half of these cases 0.5 cc of milk yielded only an occasional colony or a few colonies at best, but the other cultures showed the aureus variety as dominant.

The interesting paper by Dudgeon and Jewesbury, although not dealing with impetigo, states that "It is well to realize that infection of the infant from the mother's milk is a greater possibility than has been believed, and that valuable information may be had from the bacteriological and cytological examination of the mother's milk and infant's feces." In their review of the literature of the subject they state that remarkably little work appears to have been done on the subject. Their experience suggests that the organisms present in the milk, such as streptococci, staphylococci and colon bacilli, may at times cause gastrointestinal infection in the infant, particularly however when an actual mastitis exists.

Undoubtedly such organisms, whether pigmented or not, are saprophytic most of the time, but like other microörganisms the staphylococci have cadences of virulence of which impetigo is probably one of the pathologic manifestations. In like manner fusiform bacilli, present in many normal mouths, become virulent at times, and epidemics of such infections result. Such well-known facts should be sufficient answer to any question that might be raised regarding the presence of Staphylococcus aureus in milks of

mothers whose babes did not have impetigo. On these grounds an outbreak of infection would be almost wholly a question of virulence, which is not confined to any particular type of aureus.

This point of view is further confirmed by the fact that no serologic or epidemic type of Staphylococcus aureus seems peculiar to the disease. It seems likely, though, that pathogenically the infecting cocci have taken on some character that we have not yet learned to recognize. This may be inferred from the character of the pemphigus lesion, which is so often vesicular and leaves a weeping base. This is not the usual lesion caused by staphylococci. That it cannot be entirely explained by the age of the patient is evidenced by the superficial peeling of the fingers of nurses who become infected from the babes.

It was on such grounds that we rigidly isolated the mother of the first child of every outbreak, as detailed in our previous paper. Whether a coincidence or not, the measure was followed by results that were a contrast to those obtained by washing walls and door knobs with bichloride, fumigating rooms, employing extra nurses and so forth. Experience in this hospital seemed to justify the procedure as an addition to the *regular hygienic régime*, even though absolute scientific proof of its soundness is not at hand.

If the laboratory animal could be used as a criterion of virulence for the Staphylococcus aureus isolated from this disease the problem would be much simpler, but that it is by no means always possible to make such correlation is generally recognized. This is particularly true when feeding experiments are employed, as evidenced in our previous paper.[1] It appeared also that a culture's invasiveness at different times varies greatly, due presumably to a loss in virulence under the conditions of the laboratory. We are then faced with the problem of the origin of virulence in this rather diverse group of cocci.

Origin of Virulence: Its Relation to Bacterial Variability. When one is confronted with the diversity of types that may be isolated from the individual case perhaps, and certainly from the cases as a whole, it is customary to consider that the organisms have no primary relation to the disease or that the effects they produce are independent of the criteria which we use to separate types. Granting that the latter is probably true, can it not be reconciled first with diversity of type found? And, second, can such diversity itself be explained?

In answer to the latter question the work of Baerthlein[5] seems pertinent. He isolated four distinct types of staphylococci from one lesion. They included both pigmented and nonpigmented varieties, and were distinguishable by other cultural criteria as well as serologically. After isolating them in purity he showed that experimentally he could derive Types III and IV from Types II and I respectively, while Types I and II are serologically

closely related, even though Type I is an aureus and Type II is nonpigmented.

This diversity of type then is a result of variability within the species. It can no longer be doubted that such changes commonly occur both within and without the animal body. Furthermore, these results have been confirmed in principle by Breinl and Fischer,[6] whose induced staphylococcus variants are permanently changed as regards their serology and the Gram stain. Is this variation process, which makes for diversity of cultural and morphological type, associated with acquisition of virulence? This question has been affirmatively answered in our own laboratory on more than one occasion.

In a paper given before the American Society of Bacteriologists last December, we showed that from a strain of Bacillus alkaligenes, entirely nonvirulent, we were able to derive by variation a strain of moderate virulence as well as one of high virulence.[7] This character developed suddenly at the time the variants were dissociated, but on continued cultivation under laboratory conditions it gradually disappeared. It is of considerable interest that the strain which developed the higher virulence showed the greatest morphological difference from the other two strains, both of which were coccoid in character; yet serologically two of the strains were identical, while the third showed distinct group and specific immunological relationships. In other words, morphological and serological changes may or may not accompany variability within the species at a time when virulence is acquired.

If under the conditions of the laboratory it can thus be shown that the cyclic conditions which are involved in the biology of bacteria result in the acquisition of virulence, there is no reason why this and the reverse process should not occur in the host tissues as well. As a matter of fact, we know that such do occur. I need only cite the work of Gotschlich[8] with the plague bacillus which he isolated from a case of the disease. He recovered both a virulent and a nonvirulent type from the same case, and they were culturally quite diverse. Although the avirulent immune serum specifically agglutinated the virulent culture, at a later period the avirulent culture after standing in the icebox for some time spontaneously returned to the virulent type.

Such experimental findings give a plausible explanation why no specific serological type has been identified with impetigo. Furthermore, our serological study of impetigo strains and other staphylococci lend additional support to the position taken. From the standpoint of bacterial genetics it is probable that our specific serological types take origin from ancestral strains possessed of more than one agglutinogen. This we showed clearly in our work with Bacillus alkaligenes.[7] This means that if we can isolate such ancestral strains from the host tissue we have, so far as the

bacterium is concerned, the ready potentiality for the dissociation of new types, some of which appear to have increased virulence when first dissociated.

Our serological results with members of the Staphylococcus group have revealed clearly the existence of such strains, although the details will be reported at a later time. We have, for example, from a normal breast as well as from the gall bladder two strains of staphylococci which have never shown any pigment but which have been given every chance to do so since their isolation a couple of years ago. Their antisera, however, show that in addition to the white group they also possess antigenically an orange group, which can be absorbed out of their antisera by an orange coccus but which leaves the "white" agglutinin in the serum untouched. On the other hand, this white coccus, which we shall speak of as No. 644, will not agglutinate in the serum of the orange coccus, showing clearly that phylogenetically the latter was in all probability derived from the former. This orange strain was isolated from the skin of a babe having pemphigus and we had several more like it.

It is of note that we isolated four strains from gall bladders which apparently have mixed white and yellow antigenic groupings in them, although the strains themselves are pure-line cultures. In this case the organism was pigmented yellow or orange, yet antigenically it contained "white" receptors which agglutinated with the "white" antibodies in the antiserum of strain No. 644. These latter strains are typified by strain No. 3. We have then strains No. 3 and No. 644, examples of two groups containing mixed agglutinogens, but culturally in No. 644 the white group is dominant, while in No. 3 the yellow group is dominant. Neither strain ferments mannite which is more characteristic of the nonpigmented strains as a whole.

It is clear that the staphylococcus group is serologically fairly heterogeneous, and when one isolates a white coccus he is not sure whether he has a pure type of Staphylococcus albus or whether he has a nonpigmented aureus culture or perhaps a mixed strain which includes a pigmented antigen in its grouping. In like manner when one isolates a pigmented staphylococcus he cannot be sure that he has a Staphylococcus aureus in pure type, since this organism may contain a very definite agglutinogen for purely albus strains. With the background of the experimental work cited, it is entirely possible then to reconcile this serological diversity and the lack of a specific epidemiological type and still regard staphylococci as the pus producers they are really known to be; but it means that the virulence which certain infecting strains may seem to have has probably come about as the result of definite variation which may have involved a loss or an acquisition of pigment-producing capacity.

It is entirely conceivable that a strain of the No. 644 type growing in breast milk could dissociate its aureus component, the variation involving perhaps acquisition of virulence. In fact, certain of Baerthlein's transformations[5] with these cocci were brought about in litmus milk. The evidence is constantly increasing that these cyclic fluctuations take place with the bacteria as a part of their natural life history, and although most of the variants among such groups are probably saprophytic, the variation change *may* include the development of virulence.

Although throwing no light on the nature of virulence itself, such a conception of its origin aligns it with processes that we believe are periodically occurring with all groups of microörganisms. Fundamentally they are of an adaptive nature to preserve the life of the strain itself. The general subject of microbic heredity and the biology of bacteria has been a central interest of this laboratory for many years, and to those interested we may refer the reader to the publications indicated in the bibliography.[9, 10, 11, 12, 13]

Conclusions. 1. Normally human milk usually contains nonpigmented staphylococci and a varying percentage contain pigmented staphylococci.

2. The fact that Staphylococcus aureus is the probable cause of pemphigus neonatorum opens the possibility that the milk may in certain instances be a source of such infection, namely, when the cocci they contain are virulent for the infant.

3. It is not contended that the observations so far made are sufficient to establish human milk as a source of such infection.

4. There are ample experimental grounds for the view that the heterogeneity of the staphylococci is the direct result of variability, which is at times associated with the sudden appearance of virulence.

5. This point of view, together with the lack of any epidemiological type for the disease, makes staphylococci *from any source* potential causes of outbreaks of pemphigus neonatorum.

6. It is on such grounds that segregation of those mothers, who have been tentatively regarded as carrying staphylococci virulent for infants, has been employed.

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NYSTAGMUS: NEURO-OTOLOGIC STUDIES CONCERNING ITS SEAT OF ORIGIN.*

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Nystagmus is a phenomenon consisting of a series of rhythmic, biphasic movements of the eyes, the eyes in the first phase deviating from their position of rest or fixation and in the second phase returning to (or near) their original position. The movement in the first phase is carried out slowly and is, accordingly, designated as the slow component; that of the second phase is rapid and jerky in character, and is known as the quick component. The latter being the more conspicuous of the two phases is the one that is employed to indicate the direction of the nystagmus, so that the term "nystagmus to the right" indicates a primary deviation of the eyes to the left which is followed by a return jerk to the right, and so forth.

The phenomenon, leaving out of consideration here the nystagmus caused by visual disturbance, such as is seen in degenerative disease of the choroid and retina, as in miner's nystagmus, in which case the rhythmic movements of the eyes are rather pendular in type, is the motor manifestation of an excitatory process in the vestibular system, either at its periphery in the labyrinth, or along the course of the vestibular nerve as far up as its termination at the nucleus Deiters' and nucleus Bechterew in the pons and the nuclei tecti of the cerebellum.[1] It is not, as yet, definitely known whether excitation of the secondary afferent neurone in this system, the

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neurone which, originating at these nuclei, ascends to the midbrain as the vestibulomesencephalic tracts, is also associated with nystagmus. Experimental evidence tends to show that excitation of these tracts produces only conjugate deviation of eyes and its allied phenomena, such as rolling movements or falling to one side.[2] The excitation may be produced artificially as when nystagmus is brought about by the rotation or caloric testa of Bárány; it may be caused by irritation of the labyrinth or nerve by neoplasms, inflammatory exudates or by trauma; and it may, finally, be the result of the unantagonized activity of the intact vestibular system which results from the destruction of this system on one side, as in section of the 8th nerve on one side, in which case the nystagmus is invariably toward the normal side.

The motor manifestation resulting from such excitation of the vestibular system is not, however, always biphasic. In the lower vertebrates, as in the petromyzon, in the turtle, or the frog, it is limited to a slow deviation of the eyes which persist in their new position showing no tendency to a return jerk. This type of a reaction may be observed also in man under a moderate degree of narcosis. Deep narcosis on the other hand, when this is so profound as to suppress the corneal reflex, abolishes alike the slow as well as the quick component. These observations have led to the conclusion that the slow component is phylogenetically and ontogenetically the more primitive and elementary motor reaction, that it is consequently the more resistant of the two, and that its seat of origin is at the lower motor nuclei in the pons and midbrain (the nucleus abducens in the pons and through the medium of connecting fibers in the posterior longitudinal bundle in the contralateral nucleus oculomotorius).[2]

As to the seat of origin of the quick component it is still a moot question. Bárány believed that this component forms a part of a composite reflex which originates in its entirety in a nystagmus center which is situated, according to him, in the cerebellum.[3] Bartels[4] studying the question experimentally, concluded that the rapid phase originates in the cerebrum. This view was opposed by Bauer and Leidler[5] who from their experimental studies concluded that neither phase of the nystagmus is disturbed by the destruction of the cerebrum even when the destruction is so extensive as to include the optic thalami and adjacent structures as far down as the corpora quadrigemina.

Wilson and Pike,[6] experimenting on dogs and cats, found that the quick phase is abolished by the complete removal of the cerebrum provided such removal includes the optic thalami. A. C. Ivy[7] who carried out a series of experiments on pigeons, rabbits, cats, pups and dogs concluded that the quick phase of nystagmus is not dependent upon the integrity of the cerebrum but is determined entirely by some center below the thalamus.

Neuro-otologic Studies in Man. In an endeavor to determine this question I carried out a series of neuro-otologic studies in cases of apoplexy with hemiplegia which had as one of their symptoms conjugate deviation of the head and eyes or of the eyes alone. As it is well known, conjugate deviation of the head and eyes, or of the eyes alone, in which the eyes are directed away from the paralyzed side, in the words of Vulpian, "the patient looking at his lesion" is a phenomenon which is very common in cases of hemiplegia when these are of vascular origin. It is absent only in lesions that either are very mild or are so severe as to interfere with the activity of the intact hemisphere. The symptoms is to be ascribed to the destruction of that part of the cortex cerebri, or of its fiber tracts in the internal capsula, which controls rotation of the head and eyes or of the eyes alone toward the opposite side of the body. This laterogyric action of the head and eyes may be brought about, experimental evidence shows, by stimulation of one of two regions in each hemisphere, namely, an area which is situated in the pre-Rolandic or motor zone, more specifically, in accordance with the researches of Beevor and Horsley in the orang,[8] in the middle and inferior frontal convolutions of the frontal lobe; and another area which is situated in the sensory zone, or more specifically, in accordance with the studies of Luciani and others,[9] in the angulargyrus of the parietal lobe. The abolition of this function from one hemisphere allows, it may be assumed, the laterogyric action of the other hemisphere to come into play unantagonized and unhindered, producing in this manner a rotation of the head and eyes toward the side of the lesion. The symptom is generally pronounced for a day or two following the stroke. It then becomes progressively attentuated so that after a week or ten days it is hardly noticeable. It frequently may be detected, however, even then by the slight resistance of the patient to passive rotation of his head toward the side of the paralysis, or by his reluctance to look in that direction. This latter condition may last for five to seven days when finally either through recession of the early inflammatory reaction and the restitution of the functional integrity of the affected fibers or as a result of a compensatory action by other parts of the cerebrum, such as is presumably at play in the recession of aphasia all trace of the phenomenon is lost.

Labyrinthine stimulation during this period of conjugate deviation of the eyes when the laterogyric action of the affected hemisphere of the cerebrum is definitely in abeyance, should, I thought, accentuate the already existing deviation of the eyes but produce no rapid phase to the side opposite to the lesion, whenever the stimulation is such as would produce normally a nystagmus to the corresponding side, if the rapid phase has its origin in the motor area of the cerebrum. It should produce then no rapid phase to the side of the intact hemisphere, as well as no slow, primary deviation

towards this side, in the case such stimulation would produce normally a nystagmus to the side of the affected hemisphere, if both these phases are, like the abdominal and cremasteric reflexes, dependent upon the functional integrity of this area. It should finally, produce a normal, biphasic reaction, if both phases originate at the nuclei of the eye muscles in the midbrain and pons and are, like the pupillary reaction to light, or the corneal reflex, independent of the cerebrum.

I have accordingly studied by the caloric tests of Bárány (warm as well as cold irrigations of the ears) 16 cases of hemiplegia, with conjugate deviation of the eyes, for a variable time following the stroke.

The results of these studies are shown in the following illustrative cases:

Case Reports. CASE I.—Mrs. A. McC. (Los Angeles General Hospital, No. 19075); right sided hemiplegia of vascular origin, with both sensory and motor aphasia, conjugate deviation of eyes to the left. The patient became suddenly paralyzed in the right side of the body (lower part of the face, arm and leg) at about 6.00 A.M., January 14, 1924. She became partly unconscious then and remained in same condition until about 10.00 A.M. When examined at about 11.30 A.M. patient was fully conscious, but could not understand the simplest questions or commands, nor could she utter a word. Her pupils were unequal, the left wider. Both reacted to light. The tendon reflexes in the right arm and leg were hyperactive. The abdominal reflexes on the right side were absent. Babinski on that side but no ankle clonus. Sensation seemed to be preserved. Patient had conjugate deviation of the eyes to the left but was able to move them now and then spontaneously to the right.

Otologic Examination (this patient and two others have been examined by the author in association with Dr. Isaac H. Jones). Patient, as far as could be learned from her family, never had any ear trouble. On douching her right ear with water at 68° F. and head at 60 degrees back, the eyes after twenty seconds were drawn to the right, and there occurred a horizontal nystagmus to the left. The nystagmus had kept up for about five minutes. It was normal in rhythm and amplitude. On douching the left ear with water at 68° F., head at 60 degrees back, the eyes after twenty seconds were drawn to the extreme left angle, where they manifested a tendency toward slight nystagmus to the right. This stopped after a few moments, and in spite of prolonged douching there was no further disturbance in either eye. It was thus obvious that the motor action responsible for the quick component was either absent or, when present, was so feeble as to be incapable of moving the eyes out from the left angle. Patient exhibited no constitutional

response-pallor, sweating and nausea, although one ear was douched after the other, and the douching was kept up for a long time.

On the day following (January 15) patient's condition was much worse. When examined about 5.00 P.M., she was deeply in coma and there was no vestibular response attainable from irrigating either ear. (This patient was examined in the presence of Prof. Georges Portman, professor of otology at the University of Bordeaux, who visited Los Angeles at that time). Results identical with the foregoing—a slow component only on irrigating with cold water the ear on the side of the lesion and a more or less normal nystagmus on irrigating the ear on the opposite side (the side of paralysis) whenever this irrigation was done while the patient was conscious, and no response of any kind and from either ear if the patient during such procedure was deeply unconscious, have been obtained in all the cases so far studied. The results obtained in the patients when conscious thus show that a lesion of the laterogyric center or its conducting tracts in the internal capsula on one side, as manifested by conjugate deviation of the eyes to the side of the lesion, abolishes the quick component of nystagmus to the other side. It shows further that such a lesion does not affect, apparently, the slow component of nystagmus. This last statement may have to be modified with the further study of the phenomenon. I have gained the impression from my observation in the cases so far studied that the slow component is, to some extent, also modified by such a cerebral lesion. This component, or the primary deviation of the eyes toward the intact hemisphere which follows the cold irrigation of the ear on the corresponding side has been frequently observed to be of much smaller range than normal, and the quick component to set in before the eyes have reached the midline.

Patient died on January 30, 1924. The necropsy performed by Dr. George Maner showed the following: The pia over the whole of both hemispheres is edematous and cloudy, but thin; the convolutions are slightly atrophied and the vessels over the left hemispheres are collapsed and empty. The left middle cerebral artery just at its formation is filled with an adherent soft grayish-red thrombus. The remainder of vessels are collapsed. The lateral ventricles are symmetrical, not dilated, On section the gray matter of the optic thalamus and the corpus striatum of the left side is of a pale, dirty gray-brown appearance and of softened consistency as compared with the same area on the other side. The white matter in the internal capsule on the left side is softened and friable. Practically the whole of the brain substance of the left cerebral hemisphere is somewhat softened. Right side showed no involvement. Cerebellum, pons and medulla do not appear to be altered.

CASE II.—A. C. (Los Angeles General Hospital, No. 203698) Left-sided hemiplegia of the capsular type with slight involvement also of the right side. The rapid phase of nystagmus is practically absent on irrigating with cold water the right ear; it has a tendency to be atypical on irrigating the left ear. (This patient, it will be noted, was examined while he was unconscious.)

A male patient, aged sixty-nine years, an American, had a stroke of apoplexy with unconsciousness at about 6.00 A.M. of February 15, 1924. When examined at about 7.00 P.M. of that day patient was still unconscious. He did not utter a sound or respond to commands. He moved his right arm now and then, but none of his other limbs. The left arm and both lower limbs were definitely atonic. The tendon reflexes could not be obtained in any of these. The Babinski was positive and the cremasteric and abdominal absent on both sides. His pupils were rather small but equal and reacted promptly to light. Blood pressure was 172/115. He had a conjugate deviation of the head and eyes to the right. The eyes moved, however, now and then spontaneously toward the left as far as the midline.

Otologic Examination (in association with Dr. H. F. Linthicum). Drum membrane is intact on both sides. Douching the left ear with water at 68° F. and the 60 degrees back, produced after about twenty seconds, conjugate deviation of the eyes to the left which was followed by indefinite rolling and jerky movements to the right but no definite type of nystagmus. On repeating the irrigation of the same ear about a half hour later there set in after twenty seconds a conjugate deviation of the eyes to the left which was followed by a definite rhythmic slow nystagmus of a large amplitude and horizontal in type to the right. This was interrupted occasionally by the eyes going into conjugate deviation to the right again. The nystagmus was marked for about a minute; it then became slow and indefinite and remained so for about three minutes. On douching the right ear with water at 68° F. and head 60 degrees back, there occurred, after about twenty seconds, an accentuated conjugate deviation of the eyes to the right; this was followed by indefinite, irregular, intermittent, small, horizontal and rotatory nystagmoid movements which formed a marked contrast to the large, slow and rhythmic nystagmus obtained from the left side. The duration of this reaction was about a half a minute. Despite prolonged douching there was no nausea, vomiting or pallor. Patient's unconsciousness gradually deepened and he died about thirty-six hours later. A permit for an autopsy was refused.

In contrast to the foregoing two cases in which the cerebral lesion was extensive was the following case in which, from the clinical course it may be assumed that the lesion was limited to the pre-Rolandic or motor zone of one hemisphere.

CASE III.—C. D. (Los Angeles Hospital, No. 206314). Right-sided hemiplegia with Broca's aphasia (anarthria of Marie); conjugate deviation of the eyes to the left.

A male patient, an American, aged forty-seven years, was admitted to the hospital in a stuporous condition about 6.00 P.M. of March 28, 1924. No history of onset. When examined at about 10.00 A.M. of March 31, 1924, the patient was fully conscious. He had motor aphasia (or Marie's anarthria) which was complete, as he could neither speak spontaneously nor could he repeat words spoken to him, but his comprehension of speech was unusually good. He presented a paralysis of the lower part of the face, arm and leg on the right side. Pupils were equal and reacted promptly to light and accommodation. No difficulty of deglutition. Tongue deviated to the right. Tendon reflexes in the right limbs were hyperactive. He had a Babinski, Chaddock and a Gordon on the right side, but no ankle clonus. The cremasteric and abdominals were lost on that side. All the reflexes were normal on the left side. General sensibility seemed to have been preserved everywhere. He appeared to have had no hemianopsia. He showed a tendency to conjugate deviation of the eyes to the left, but was well able to move his eyes to the right.

Otologic Examination (this and the remaining 11 cases have been studied by the author in association with Drs. Homer S. Keyes and J. M. Neilson, resident physicians at the Los Angeles General Hospital). Drum membrane is intact on both sides. Irrigating the right ear with water at 68° F. and head 60 degrees back, produced after twenty second a conjugate swing of the eyes to the right which at the time they reached the midline and before entering the right half of the eyes, began to show a nystagmus to the left, the rapid phase, which was horizontal in type, rhythmically pulling the eyes into the left canthus. This lasted for about three minutes. On placing the patient in an upright position, with head 30 degrees forward, the nystagmus becomes rotatory in character but continued to be to the left (the normal reaction for this position). The constitutional response following the irrigation was very severe. On irrigating the left ear with water at 68° F. head 60 degrees back, there set in after about twenty seconds an increase in the pre-existing conjugate deviation of the eyes to the left. This was followed by a few oscillatory movements to the right which quickly ceased, the eyes remaining in a position of deviation to the left, although the irrigation was kept up for nearly five minutes. On placing the patient upright with the head 30 degrees forward, the eyes continued to stay in this position. During the irrigation of this ear a tendency was noted on the part of the eyes to become dissociated in their direction of fixation, the homolateral eye remaining deviated in the left and the right eye moving toward the right and remaining near the midline. This dissociation in the position

of the eyes while irrigating with cold water the ear on the side of the lesion was noted in a number of instances. It suggests the possibility that in the laterogyric action of the eyes each hemisphere inervates more powerfully the contralateral eye, hence this persistent deviation in above quoted case of the left eye to the left, than the homolateral eye which showed a tendency to move to the right. The constitutional response following the irrigation of the left ear was distinctly subnormal. The patient was reëxamined on April 2 and again on April 5. He was able then to move his eyes voluntarily in all directions, but when at rest, the eyes tended to become conjugately deviated to the left. His general condition showed considerable improvement. He was quite alert and coöperated in his examination with intelligence. He was able to speak a few simple words although he mispronounced them. The otologic studies on either of these dates gave results which were in all respects identical with those obtained on March 31. He was reëxamined on April 14 and again on April 16. On these dates he showed no conjugate deviation of the eyes but when asked to look to the right he showed a tendency to turn his head in that direction instead of turning his eyes that way. His general condition was then very good. He walked around with comparative ease and while dysarthric was able to express his wants in sentences. The otologic examination showed that there was still a striking difference between the nystagmus obtained on caloric stimulation of the right labyrinth and that obtained from the left. The nystagmus obtained on the cold irrigation of the left ear, was oscillatory and pendular in character and its duration was short, whereas that obtained in the same manner from the right ear, while frequently modified, was more or less of the normal type. This difference has, moreover, been noted in several instances as late as three months following the apoplectic stroke, a fact of much practical importance. The physician in carrying out the labyrinthine tests on a patient with a hemiplegia of recent onset in an endeavor to determine the condition of the vestibular system should bear this fact in mind, as on an impaired nystagmus to the side of the paralysis obtained in such a patient may be due entirely to the cerebral lesion and in the absence of any trouble whatever in the labyrinthine mechanism.

The impairment of the nystagmus caused by the cerebral lesion is not, however, it appears from the studies I have so far made, a permanent phenomenon. It tends to recede, and in about six months following the stroke practically no difference is to be detected in the phenomenon as obtained from either labyrinth.

Addendum.

I recently had an opportunity to study the vestibular responses in a case of unilateral convulsions with conjugate deviation of the

head and eyes—a condition which represents the direct opposite to that of apoplexy with hemiplegia. The report follows:

CASE IV.—(No. 221992). A male patient, aged thirty-four years, with taboparesis, was admitted to the psychopathic department of the Los Angeles General Hospital, on January 16, 1925. I examined him in association with Drs. Eshman, Calvert and Sugar, resident physicians at the hospital, at about 6.30 P.M. of January 22, 1925. He was then in coma and had convulsions of the clonic type which involved the leg, arm, and face on his right side. His head and eyes were turned to the right, in the direction opposite to the hyperactive motor cortex of the cerebrum. His eyes moved, however, spontaneously now and then to the left. The patient, it was reported, had never had any ear trouble. Labyrinthine stimulation, while he was in this state, by the cold caloric to the right ear produced an accentuated conjugate deviation of the eyes toward the right but no rapid movement toward the left. Stimulation of the labyrinth by the cold caloric to the left ear gave rise, on the other hand, to a normal, biphasic reaction toward the right. The nystagmus so obtained from this ear was of large amplitude, horizontal in direction (the irrigation having been done with the patient in the recumbent position with his head at 60 degrees back) and lasted for a minute following the cessation of irrigation, (two and a half minutes).

I reëxamined him on February 22, 1925. He walked around then in a normal manner and was fairly clear mentally. Neurologic examination showed the following:

Argyll-Robertson pupils. Ocular movements normal. No spontaneous nystagmus. Fundi were normal. Speech was tremulous, paretic. Deep reflexes in arms and legs lost. Cremasteric and abdominal reflexes were present on both sides. No Babinski on either side. Hearing was excellent in both ears.

On stimulating his labyrinths with cold water a rhythmic, biphasic reaction, the rapid phase of which was toward the side opposite to the ear irrigated, was obtained from either side. The amplitude of the nystagmus so obtained from the left ear (from the side corresponding to that of the hyperexcitable and hyperactive motor cortex) was, however, much greater than that of the nystagmus from the right ear.

There was similarly a great difference between the pastpointing reactions from the two sides. Whereas on irrigating the right ear the initial range of the pastpointing by the right arm to the right was 3 inches, that of the left arm to the left on irrigating the left ear was 12 inches.

The reactions on stimulation of either labyrinth were obtained from the horizontal canals only (when the head of the patient was at 60 degrees back), no response having been obtained from the vertical canals (when the head was at 30 degrees forward).

Conclusions. 1. In cerebral hemiplegia of vascular origin during the period of conjugate deviation of the eyes to the side of the lesion it appears to be impossible to evoke nystagmus to the side opposite to the lesion. Labyrinthine stimulation of a character which evokes this reaction to the corresponding side in a normal person produces instead—provided the patient is not deeply unconscious, a persisting and frequently intensified conjugate deviation of the eye to the side of the lesion.

2. The substitution in this condition of nystagmus by conjugate deviation of the eye to the side of the lesion, or merely an impairment of the nystagmus, may outlast by months the conjugate deviation of the eyes which as an initial phenomena was brought about directly by the cerebral lesion, a fact to be remembered in evaluating the atypical nystagmus resulting from stimulation of the labyrinth in patients with a recent hemiplegia.

3. The motor impulse for the rapid phase of nystagmus originates in the cerebrum. The fact that it was found to be abolished by lesions which gave rise to hemiplegia with pure motor aphasia, and no phenomena referable to the sensory cortex or optic thalamus makes it highly probable that it has its origin in the laterogyric center of the eyes, which is situated, in accordance with the researches of Beevor and Horsley, in the middle and inferior frontal convolutions, in an area adjacent to the speech center of Broca. The corpus striatum undoubtedly play a part in the production of this phenomenon. In a case which I reported in a previous publication[10] and in which microscopic study of the brain showed degeneration of the globus pallidus and no lesion of the motor cortex, pyramidal tracts, optic thalamus, midbrain or pons, labyrinthine stimulation produced a nystagmus which was normal in direction and amplitude but greatly lessened in duration, the eyes showing a tendency to persist in the primary phase of the nystagmus—the conjugate deviation.

4. The motor impulse for the slow phase of nystagmus originates, most probably, in the nuclei of the eye muscles in the midbrain and pons. It may be produced by appropriate stimulation of the labyrinth to either side, regardless of the cerebral lesion. It appears highly probable however, that this phase is to some extent also influenced by cerebral activity.

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REVIEWS.

WILLIAM CRAWFORD GORGAS: HIS LIFE AND WORK. By MARIE D. GORGAS and BURTON J. HENDRICK. Pp. 359; 10 illustrations. Philadelphia and New York: Lea & Febiger, 1925. Price $5.00.

WITHOUT doubt the greatest feat that American medicine has yet achieved is the discovery of the cause and method of transmission of yellow fever and its extermination in this continent. Equally without doubt General Gorgas is the one individual to whom chief credit is due for the achievement of the last-named feat. In fact if it had not been for Gorgas' invincible determination to apply Reed's discovery, in spite of all obstacles, the authors assure us that the latter might long have remained an unfruitful academic achievement. It has become a truism to state that control of the stegomyia alone made possible the building of the Panama Canal and yet this epochal event was only the dramatic first fruit of labor which Gorgas hoped (and not without reason) would soon eradicate this former scourge from the globe.

The lack of shadow contrast in the tale is pardoned by the reader in return for the exalted enthusiasm which sweeps through the book; and if other actors in the most important scene of the play have not quite received their due, there is glory enough for all and their turn will come later if it has not already been recorded elsewhere.

The life history of this "ragged, barefoot little rebel" from Baltimore, who so accomplished his inspired duty that "his name will shine for ages in the history of our race," is most attractively told by the one best qualified to know, working with one of the best biographers of our day. And the results are all that one might hope for. One finishes the volume only too quickly, and is at a loss whether to admire more the winning personality of the man or the sterling qualities of the administrative genius. Surely if contemplating the lives of eminent contemporaries is one of the surest sources of inspiration, this volume should be read by every student of medicine—graduate and undergraduate. E. K.

DIABETIC DIET. A HANDBOOK FOR DIABETICS. By A. DORIS MCHENRY, B.A., and MARJORIE M. COOPER, B.A. Pp. 62. New York and London: Harper and Brothers, 1925.

THIS little book is recommended chiefly by a goodly number of recipes that will be found valuable in constructing and varying the

diabetic's diet. In addition there are brief chapters on the composition and value of food, methods or urinalysis, weights and measures, and the general plan of diabetic diets with sample menus. The sample diets as given are open to some criticism. Too great a percentage of carbohydrate is given in the form of fruit or milk sugar. Thus in a very restricted diet containing only 30 grams of carbohydrate, two-thirds of this is given in the form of orange, grapefruit and milk. In another diet containing 98 grams of carbohydrate, no 15 or 20 per cent starch-containing vegetables are used but whole wheat bread and apples are included. R. K.

PHYSICAL DIAGNOSIS. By W. D. ROSE, M.D., Lecturer on Physical Diagnosis and Associate Professor of Medicine, University of Arkansas. Fourth edition. Pp. 755, 319 illustrations. St. Louis: C. V. Mosby Company, 1924.

IN the fourth revised edition of this work the author has continued in his original purpose to write a text for the student and general practitioner. This he has done quite successfully. Physical examination of thorax and abdomen are well and completely covered. A few minor details might be criticized. For instance, auricular fibrillation is still described as an unsystematized fibrillary twitching of the auricular muscle and no mention is made of the fairly well established views in regard to circus movement in this condition. In describing the physical signs of massive pulmonary collapse no mention is made of the displacement of mediastinal structures. In the main the treatment of the subject is adequate. The chapter on Examination of the Nervous System is not full enough. The book is profusely illustrated; some of the illustrations are good but many of them are rather poor, due to the quality of paper rather than poor photography. R. K.

COMMON INFECTIONS OF THE FEMALE URETHRA AND CERVIX. BY FRANK KIDD, M.A., M.CH. (CANTAB.), F.R.C.S.(ENG.) And A. MALCOLM SIMPSON, B.A., M.B., D.P.H. (CANTAB.). With additional chapters by GEORGE T. WESTERN, M. D., and M. S. MAYOU, F.R.C.S. Pp. 183: 9 illustrations. London: Humphrey Milford, Oxford University Press, 1924.

THE reviewer feels the authors have indeed achieved the main objective of the book, namely, the description of simple methods of treatment of gonococcal and other infections of the female urethra

and cervix which will be within the scope of the general practitioner to apply, for it is to general practitioners that the majority of such cases will present themselves. The book is well planned and well written. It is based upon clinical observations made since 1917 in a new department of the London Hospital. The descriptions of various infections are concise, the methods of treatment are detailed, and the additional chapters by the co-authors are excellent supplementary resumes of bacteriology and ophthalmia. While perhaps intrauterine medication in acute pelvic inflammatory disease may not be accepted in America, yet the findings of the authors seem to show its merit. One is surprised at the omission of any reference to the tracheloplastic operation of Sturmdorf for chronic endocervicitis.

P. W.

GYNECOLOGY, MEDICAL AND SURGICAL. By P. BROOKE BLAND, M.D., Assistant Professor of Gynecology, Jefferson Medical College; Assistant Gynecologist, Jefferson Medical College Hospital; Gynecologist, St. Joseph's Hospital. Pp. 1257: 644 illustrations. Philadelphia: F. A. Davis Company, 1924.

THE volume in hand, the Students Edition, is bulky and heavy, and one is pleased to learn that another edition, the Library Edition, is published in two volumes, presumably more easily handled. In presenting this compilation, the author frankly states in the preface that there is no claim to anything especially new, to which the reviewer agrees. That a scarcity of books upon this subject could have been responsible for the production of this work is to be doubted, for several excellent works are referred to in the preface.

The subject matter follows the arrangement of Dr. Montgomery's well-known textbook, morbid conditions being classified pathologically rather than anatomically, and the text is quite well up with the most recent of the ever-changing opinions and literature in gynecology. Many of the illustrations are excellent, some are poor. A certain sense of disproportion is felt here and there, as witness the seven pages devoted to the details of the Wassermann reaction compared to a scant page or more on the treatment of sterility.

P. W.

AN INTRODUCTION TO DERMATOLOGY. By SIR NORMAN WALKER. Eighth edition. Pp. 373; 92 plates and 80 illustrations. New York: William Wood & Co., 1925.

THE author makes no pretense at presenting a complete system, and for the purpose intended, namely a text for students, his book

is a success. The refreshingly direct, rugged style of the author must at once influence the dermatologist in favor of some of the radical positions that he frequently takes. Thus, the subject of eczema finds no place in the book; it has gone by the board in keeping with the ideas of Highman, in this country, and others. "Dermatitis" takes its place. As to the illustrations, many are so excellent that it is hard to understand how the author could admit so many poor ones. This applies to the colored plates as well as to the other illustrations.

On the whole, the book surpasses many American ones as a teaching medium for students, but it cannot rank with them in value to the dermatologist or general practitioner.

F. W.

SELECTED MEDICAL PAPERS OF ALFRED WORCESTER. Pp. 339, 7 illustrations. Boston: The Four Seas Company, 1925.

THE eighteen articles reprinted in this book were published as a surprise to Dr. Worcester, in order "not only to pay a just tribute to a great physician and give pleasure to Dr. Worcester's friends, but to put in available material which will be of assistance to . . . historians." E. K.

THE TREATMENT OF FRACTURES IN GENERAL PRACTICE. By C. MAX PAGE and W. ROWLEY BRISTOW., St. Thomas's Hospital, London, England. Pp. 235; 141 illustrations. New York: Oxford Medical Publications, American Branch, 1923.

THE aim of this book is to present to the working medical profession a small, handy volume that deals simply and clearly with the practical side of the treatment of fractures. It takes up the question of, first, the diagnosis, the repair, the complications and the general principles. Subsequent chapters consider in detail the separate fractures that are met with in the human subject. The most modern ideas in the treatment of fractures are well presented and also well illustrated.

Since the general public has become more critical of the terminal results in fractures and have at their disposal the roentgen ray to show poor or good position, the practitioner at large must have a good working knowledge of fractures. This little book gives all that the average case of fracture requires. It is of handy size, its thought well expressed and the subject matter presented in an agreeable style. E. L.

La Sifilide Ignorata e Strana. By Prof. Carlo Martelli, Docente di Anatomia Patologica e Clinica Medica nella Universita di Napoli, Socio della R. Accademia Medico-Chirurgica. Second edition. Pp. 642; 73 illustrations. Napoli: Casa Editrice Libraria von Idelson, 1923.

While this volume on unsuspected and atypical syphilis will naturally not have a wide demand in this country, nevertheless its merits are such that it should be available to anyone wishing to look into the subject more thoroughly than is possible in textbooks on syphilis. In the first third of the book, are discussed general biological and clinical considerations on syphilis as a whole; in the second third, the clinic of 14 types of unsuspected or atypical syphilis (febrile syndromes, cardiovascular syndromes and so forth); and in the last third, their diagnosis, prognosis and therapeusis. A bibliography of 50 pages adds to its value to students of all nationalities. E. K.

Serum Diagnosis of Syphilis by Precipitation. By R. L. Kahn, M.S., Sc.D., Immunologist, Bureau of Laboratories, Michigan Department of Health. Pp. 237; 3 plates; 55 tables. Baltimore: Williams & Wilkins Co., 1925.

This volume records the experiments conducted during the past three years by the author on the precipitation phenomenon in syphilitic serum, and presents the details of the development, the standardization and the clinical applications of the Kahn test. the greater part of the material included has appeared from time to time in the author's publications, but its presentation in this book enables the reader to correlate the various procedures and to get a better grasp of the significance of the test. The book gives one an idea of the enormous amount of work performed in the development and standardization of this test. Underlying theories are discussed only insofar as they have practical applications. Special attention is given to the necessity for observing strict precautions in the preparation of the antigen and rigid observance of the technic in order that consistent results may be obtained in different hands. The parallelism between this precipitation test and the Wassermann test in the author's laboratory is well demonstrated.

The book is of interest primarily to serologists, and secondarily to those engaged in the study of the effects of the different procedures in the application of specific chemotherapy in the treatment of syphilis. J. S.

PROGRESS

OF

MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

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ROGER S. MORRIS, M.D.,

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Notes on the Therapeutic Value of Pneumococcus Antibody Solution Subcutaneously Administered in Lobar Pneumonia.—In view of the fairly extensive use of Huntoon's antibody solution in the treatment of pneumonia, the report of OLIVER and STOLLER (*Arch. Int. Med.*, 1925, **35**, 266) will prove of interest. They obtained the following results in a series of 23 patients to whom the solution was given subcutaneously: A low incidence of thermal reactions; a painful tissue reaction, persisting at times for days; a subjective and objective improvement in 4 cases and no benefit in 19 cases; failure to sterilize the blood; inferiority of the antibody solution as contrasted with pneumococcus antiserum in Type I pneumococcus infection; failure to prevent extension of the pneumonic process from one lobe to another; and a benefit in Type IV pneumococcus pneumonias as compared to the control cases. Additional results from the use of this solution should be published by other observers, as it is only from a study of statistics in the mass that the results of a therapeutic procedure of such promise may be properly evaluated.

Pancreatic Enzymes in Cholecystitis.—G. M. PIERSOL and H. L. BOCKUS (*Arch. Int. Med.*, 1925, **35**, 204) employ the method of Einhorn in estimating the pancreatic enzymes in cases of cholecystitis. They claim that this is a simple quantitative method probably as accurate

as any so far devised. It would seem from a study of their results and their tables that the method can hardly be called truly accurate and the impression must not be given that the method or their results are in any sense specific but rather simply additional data which are of use in evaluating the other signs and symptoms of gall bladder infection. They found that a definite reduction in the amount of pancreatic enzymes is additional corroborative evidence in favor of cholecystitis. The average amount of reduction of the enzymes was over 50 per cent in 85 per cent of their 40 cases of cholecystitis.

Contributions to the Pathology of Experimental Virus Encephalitis. II. Herpetic Strains of Encephalitogenic Virus.—S. FLEXNER and H. L. AMOSS (*Jour. Exper. Med.*, 1925, **41**, 233) have had the opportunity of working with the Levaditi strain of herpetico-encephalitic virus. They have contrasted its action with that of a pure strain of herpes virus which they have called the H. F. strain. They find that this strain is highly encephalitogenic. This is, in their opinion, of great theoretical and practical importance. The fact that such a strain exists, which is even more irritating to the central nervous system than that of the Levaditi strain, would tend to show that the criteria upon which Levaditi advocates this strain as the cause of lethargic encephalitis are not sufficiently exact to warrant his assumption. Flexner and Amoss feel that this is a virus which is probably herpetic in origin. They maintain that there exist weaker and stronger strains of virus which are probably always herpetic in origin and that it is undoubtedly the stronger strains which have been isolated in reported cases of epidemic encephalitis and which are not the true cause of the disease. Epidemic encephalitis is associated accidentally with this group of viruses at times and they bear no casual relation to the disease.

All-day-blood-sugar Curves in Nondiabetic Individuals and in Diabetic Patients with and without Insulin.—One of the difficulties in the use of insulin has been to space satisfactorily the doses of insulin. The present paper by JONAS, MILLER and TELLER (*Arch. Int. Med.*, 1925, **35**, 289) reports a series of 34 blood-sugar-concentration curves made in periods up to twenty-four hours. Their results are so valuable and put so succinctly that they are worth quoting at least in part. "A series of 34 blood-sugar-concentration curves were made on 29 patients, 6 nondiabetic and 23 diabetic, and covered periods up to twenty-four hours. This was done in an effort to work out a more satisfactory routine method of regulating the dosage and the time of administration of insulin to diabetic patients. The ideal method of distributing insulin was not arrived at, but the following general rules for the management of such cases seem warranted: (*a*) With a maintenance diet equally distributed among the three meals of the day, mild cases of diabetes may be kept within the normal limits of glycemia by means of a single dose of insulin administered a half hour before breakfast; (*b*) more severe cases require, in addition to an adequate morning dose, a second but somewhat smaller one a half-hour before the evening meal; (*c*) when the morning fasting level of blood sugar cannot be kept below the threshold value for glycosuria by these 2 doses, a third one is indicated at about midnight; (*d*) the amount of

insulin to be administered at each time must be determined by blood-sugar estimations made before and after the meals. When insulin is used, as suggested in the foregoing, the highest point may be attained before the first insulin administration of the day or an hour after breakfast, while the lowest point is usually reached just before the midday meal or in the midafternoon. In all cases of diabetes, the single specimen of urine which is most likely to show sugar is one voided from one to two hours after breakfast."

Leprosy Work at Culion.—General Leonard Wood, Governor-General of the Philippines, has recently sent out a circular letter which embraces several reports on the colony at Culion by different observers. These reports are of interest because they give some idea of the size and of the difficulty in administrating this huge leper colony. Medical men in this country may in many instances be unaware that on the island of Culion, P. I., the Government of the Philippines has segregated in a colony some 4100 lepers. Here the lepers are absolutely isolated from the well, they are given modern treatment and all their wants are amply provided for. For those who have the inclination, the will and the strength, an opportunity is given to engage in light farming or in some trade, and for the children good schools are provided. Of particular interest to the physician is that since sufficient funds for adequate treatment have been provided, more than 200 patients have been discharged as negative, 56 per cent are improved and 36 per cent are stationary. The majority of deaths are not from leprosy but from some intercurrent infection, usually tuberculosis or nephritis. One of the great obstacles that those responsible for the segregation of lepers have to contend with, is the more or less organized effort by a sentimental minority to do away with segregation. The argument is that the disease is one of the least contagious of diseases and that isolation is not necessary. It would be advisable for medical men to combat this impression whenever met. It is true that contagion is relatively difficult, but every case of leprosy is a potential focus for the dissemination of the disease and if the disease is ever to be eradicated all these foci must be segregated from contact with the healthy.

The Influence of Food Intake on the Enzymatic Concentration of Human Intestinal Contents Obtained from a Duodenal Fistula.—A young adult negro, aged twenty-three years, was admitted to the Charity Hospital, New Orleans, with a gun-shot wound of the abdomen. He was operated upon, but a few weeks later developed a duodenal fistula. As a result of this train of events, the opportunity presented itself to D. N. Silverman and W. Denis (*Arch. Int.*, 1925, **35**, 357) to study the influence on the pancreatic secretion of different foods taken by mouth under conditions uninfluenced by extraneous factors such as the presence of the duodenal tube in the stomach. A summary of the findings are most suggestive. Milk, which contains fat, protein and carbohydrate, stimulated the secretion of protease and lipase. Fat, in the form of cream, brought about a distinct stimulation of the amylase and protease within twenty-six minutes and twenty minutes later a marked increase in the lepase concentration. Almost pure protein, eight egg whites and one yolk, produced the most pronounced

reaction and all three of the enzymes reached the maximum concentration of any of the experiments. In seventy-seven minutes the amylase and protease had almost doubled their concentration and the lipolytic activity rose from 0 to 1.55 cc. Arrowroot biscuits, as a test for starch stimulation of pancreatic enzymes, caused only a slight stimulation of amylase production and but little more on protease.

SURGERY

UNDER THE CHARGE OF

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Lesions of the Tibial Tubercle. (Osgood, Schlatter's Disease).—POMERANZ (*Amer. Jour. Surg.*, 1925, **39**, 17) says that the present conception of the disease is varied. As a result of the somewhat acrimonious debate, chiefly in the German literature, both infection and trauma have been postulated as causative factors. As is well known a periostitis may be produced by local injury or local infection. There are therefore three causes, all different, each of which may be productive of a similar roentgenographic appearance. Avulsion of the pretibial tubercle occurs most frequently in the adolescent. The disease is more common than is generally supposed. The absence of acute symptoms explains the scarcity of case reports. The architecture of the joint is such as to safely withstand moderate trauma. Most of the cases comprising this report occurred in males and in the left knee, which is at variance with reports of other writers. The lesions are most commonly traumatic, although 2 cases of the infectious type are here reported. Dense reactive sclerosis occurs in old lesions. The types of cases vary according to severity of trauma from simple strains or avulsions of the periosteum to complete avulsion of the tubercle with fragmentation of this process.

Pathogenesis of Skeletal Tuberculosis.—KOLODNY (*Jour. Bone and Joint Surg.*, 1925, **7**, 53) states that the result of his investigation in relation to the most frequently involved skeletal regions in tuberculosis speak in a simple and positive way for the embolic theory of the pathogenesis of bone tuberculosis. When the blood supply is richer, other features being equal, there is a greater possibility of tuberculous involvement and hence the primary focus in these regions is more frequent. The constant strain and stress, even of a physiologic nature, has something to do as an etiologic factor in bone tuberculosis. It is evident that tuberculosis most frequently affects those parts of the skeleton which are especially adapted to the function of support and locomotion of the body, and which are under almost permanent physiological strain.

Acute Pancreatitis.—MOYNIHAN (*Ann. Surg.*, 1925, **81**, 132) believes that acute pancreatitis is the most terrible of all the calamities that occur in connection with the abdominal viscera. The suddenness of its onset, the illimitable agony which accompanies it and the mortality attendant upon it, all render it the most formidable of catastrophies. The clinical picture presented by a case of acute pancreatitis is quite unmistakable. The first and chiefest symptom is pain and of all the pains that the human body can suffer, this is by far the worst. The pain is remarkable in that it comes so frequently after a good meal. It is of the fiercest intensity in the epigastrium but it is felt also in the back and often in both loins. The patient is prostrate, faint and pallid and suffers indescribable anguish. The pulse may be hardly perceptible, the limbs and face are cold and death itself seems imminent. There is all the collapse that even the greatest hemorrhage could cause and more than the agony of a visceral rupture. Tenderness is more acute above the umbilicus than below and often is far more exquisite to the left of the middle line than to the right, a point not without significance. The rarity of the condition is stressed. The anatomic and physiologic researches of Mann and Archibald are fully analyzed.

Roentgenological Aspects of Brain Tumors: Meningiomas.—SEAMAN and PUTNAM (*Am. Jour. Roentgenol.*, 1925, **12**, 1) say that the pessimism in regard to the possibility of localizing cerebral tumors (exclusive of pituitary tumors) by roentgen examination is doubtless founded on the impossibility of visualizing them directly in the great majority of cases. The roentgenological findings in a group of 95 verified intracranial meningiomas have been reviewed. Approximately half of these cases showed recognizable changes characteristic of tumors. The bony changes, considered characteristic, are: Erosion and vascularity, spicule formation, diffuse thickening and enlargement of the meningeal channels. These changes are most frequently and clearly seen in meningiomas of the vault. Tumors about the sella are apt to cause a nonspecific distortion and destruction of the clinoids. Tumors of the base are often accompanied by a diffuse thickening of the floor of the skull. Those arising from the falx, from about the sella or from the sinuses of the posterior fossa, are least likely to give any indication of their presence.

A Case of Cerebral Abscess Complicating Abscess of Lung.—BARLING (*Lancet*, 1925, **1**, 121) believes abscesses are nearly always in the hemisphere and often near the cortex, but have been found in the cerebellum, medulla or pons. Schorstein points out that in his collected cases, the left side of brain is affected more than twice as frequently as the right. There is pathological obscurity surrounding the association of brain abscesses with lung disease. The predominance of left-sided abscesses is in favor of the embolic origin of the infection and may be compared to a like preponderance of left-sided brain infarcts in valvular disease of the heart. The abscesses are sometimes single, sometimes multiple. Metastatic brain abscesses in general appear to be more commonly multiple, but in the group of pulmonary cases the single abscesses appear to predominate. The debilitated condition of the patient, the difficulties of localization, which are undoubtedly greater than in case of traumatic or otitic abscesses, are all against a successful

result. At the same time, when the postmortem findings in a number of these cases are studied, one cannot help feeling that some might have been cured had they been operated upon.

Acute Dilatation of Stomach and Intestinal Tube with a Consideration of "Chronic Duodenal Ileus."—ROBERTSON (*Surg., Gynec. and Obst.*, 1925, **40**, 206) says that the acute cases can be divided as follows: Those in which the dilatation occurs without any apparent cause and in which, after death, no other lesion is found; those in which, after death, some definite lesion is found; those in which the dilatation follows some surgical operation and in which, after death, no other lesion is found; those in which dilatation follows an injury. The condition known as chronic duodenal ileus has been brought prominently before the profession of late. It is attributed to the constricting pressure of the superior mesenteric vessels as they cross the duodenal wall. It is indicated by a series of symptoms; obstinate dyspepsia with fulness after eating, frequent attacks of bilious vomiting, migraine, constipation, loss of weight and general abdominal discomfort. It is said to be a prominent feature of general visceroptosis. The operations proposed for it vary from a fixation of a mobile cecum to an anastomosis of the gut across the main trunk of the vessel or mesenteric root—a duodeno-duodenostomy. The author feels strongly that the "superior mesenteric artery pressure theory" will fade until it disappears entirely. Consequently he is opposed to this operation.

THERAPEUTICS

UNDER THE CHARGE OF

SAMUEL W. LAMBERT, M.D.,

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Protein Therapy and Surgical Treatment of Gastric and Duodenal Ulcers.—From the treatment of 300 cases in three years PRIBRIM (*Deutsch. med. Wchnschr.*, 1925, **4**, 141) concludes that protein therapy should be tried in all cases of gastric or duodenal ulcer. The theoretical basis for this form of treatment rests on the fact that inflammatory tissue has an increased susceptibility to irritation and the focal reaction which occurs after protein injection results in the healing of the ulcer and also on the belief that the irritability of the sympathetic nerve supply to the stomach is diminished with a resulting increase in the circulation of the ulcerated area. Practically, after protein therapy there is relief of pain and spasm, and a more rapid emptying of the stomach, which permits a quicker resumption of a full diet. The best results can be expected in ulcer of the lesser curvature, and in old indolent ulcers, and ulcers situated near the pylorus, although the latter show a tendency to relapse. Duodenal ulcers also show a greater tendency to relapse, and require more frequent courses of treatment. From 50 to 70

per cent of all ulcers can be satisfactorially treated by protein injection. Postoperative jejunal ulcers are not successfully treated. Recent hemorrhage is not a contraindication; on the contrary, hemorrhage may be checked. Chronic bleeding duodenal ulcers require radical resection. Acute or subacute tuberculous processes are absolute contraindications to this form of therapy. Pribrim's conclusions are drawn from the intravenous injections of Novoprotin (Grenzach). Doses from 0.1 cc to 1 cc are given at two- or three-day intervals, and the dose should be large enough to give a focal reaction without objectionable symptoms. A course of treatment consists of not more than ten injections and after a rest of four to six weeks another course is begun. If after two or three courses of treatment there is not distinct improvement with absolute freedom from pain, ability to work and eat a regular diet, surgical treatment is indicated.

Further Report on the Combined Calcium-digitalis Treatment of Cardiac Patients.—Since the original report of GUSTAV SINGER (*Therap. Halbmonatsch*, 1921, No. 24) on the combined calcium digitalis treatment of cardiac cases almost all cases of cardiac decompensation in his clinic have been so treated, and HELLMANN and KOLLMANN (*Therap. d. Gegenw.*, 1924, **10**, 444) report the results and the advantages of this form of therapy. As most of these cases require prolonged digitalis therapy cumulative poisonous effects and toxic symptoms frequently develop. When combined with intravenous calcium injections digitalis can be given over long periods without the usual signs of digitalis poisoning. In addition to the usual cases of cardiac decompensation due to myocardial changes they have also successfully treated patients with high blood pressure and cardiac decompensation, and cases of decompensation due to lesions of the aortic valve. Ampules containing a 10 per cent sterile solution of calcium chloride (Merck) were used. Of this solution ½ cc, 2 cc to 5 cc were injected intravenously, while digitalis was administered by mouth or given intravenously if necessary. The frequency of administration and the amount of calcium given varied with the clinical condition of the patient, but from 0.1 gm. to 0.5 gm. was usually given every other day. As calcium is eliminated by way of the intestinal tract marked constipation must be prevented by enemata or administration of magnesium.

Some Observations on Blackwater Fever.—Blackwater fever is the result of malignant tertian malaria and CARMODY (*Brit. Med. Jour.*, 1925, **1**, 106) reports the results of the treatment of 36 consecutive cases. He believes that a chronic anemia due to the malarial infection is fulminated by some sudden lowering of the patient's vitality; this leads to a temporary rapid hypotonic osmotic condition of the blood plasma, and bursting of the red blood corpuscles with the resultant characteristic dark urine. The successful treatment of this condition depends particularly on taking care not to move or shake the patient, and the immediate subcutaneous injection of normal saline solution. Five to ten ounces of normal saline are injected subcutaneously and repeated if necessary, but the urine usually clears quickly after the first injection. He then prescribes ½ to 1 ounce of magnesium sulphate to be taken at the beginning of the attack and every hour 20 gr. of

bicarbonate of soda are given by mouth. Quinin is not given as a rule, but if acute symptoms of malaria are present it is best given by intramuscular injection. Even in the mildest cases the patient should be kept in bed for at least fourteen days. Of three deaths in the 36 cases reported by Carmody only one was due to blackwater fever, and as the result of moving the patient on the third day of the disease.

Iodin in Exophthalmic Goiter.—Although the exact knowledge of the etiology of goiter is still unknown the pathology of exophthalmic goiter shows an irregular and exaggerated hyperplasia of the thyroid gland, and in such cases the iodin content of the gland is extremely low. FRASER (*Brit. Med. Jour.*, 1925, **1**, 1) reports the results of the administration of iodin to 24 cases of exophthalmic goiter and concludes that iodin may cause a decided, but temporary improvement in the objective and subjective symptoms, but that the dose must be small and carefully regulated. He used a 10 per cent tincture of iodin without the addition of iodide and gave at first 15 minims a day. As soon as improvement was noticed this amount was reduced to 3 to 6 minims daily, regulating the amount according to the condition of the patient. With this treatment there was a lowering of the basal metabolism, reduction of the heart rate, and increase of body weight, and improvement in the general condition of the patient. Large doses were shown to be harmful, but the smaller doses could be given almost indefinitely and when combined with surgery the results were striking. Iodin administration in exophthalmic goiter would justify the view that there is an iodin deficiency in this condition relative to the needs of the body.

PEDIATRICS

UNDER THE CHARGE OF

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OF PHILADELPHIA.

Celiac Disease (Chronic Intestinal Indigestion).—SAUER (*Am. Jour. Dis. Child.*, 1925, **30**, 155) outlines the care of these cases. He feels that hospital care is obligatory, if proper nursing care and coöperation cannot be obtained at home. The patient should be kept in bed until the weight exceeds by several pounds the child's maximum weight before the illness began. Extremes in room and outdoor temperatures should be avoided, and the bedding and clothing should be suitable for the season of the year. He recommends a simple high protein diet which is low in carbohydrate and fat divided into three phases. He first gives concentrated protein milk exclusively. In the second phase there are added to the protein milk certain protein foods such as curds of buttermilk or of skimmed milk, buttermilk, eggs, lean meat and boiled tongue. During the third phase there are cautiously added dextrinized starches such as flour ball, patent barley flour, imperial

granum, arrowroot crackers, and later finely rolled zwieback or toast, and finally powdered spinach and such sugars as dextrose, dextrimaltose and corn syrup. The number of calories must be ample to ensure a continuous gain in weight. This would require of from 40 to 60 or more calories in twenty-four hours. At first the number of level packed tablespoonfuls of powdered protein milk should approximate the number of pounds the child actually weighs. Gradually this is increased to approximate the theoretical number of pounds the child should weigh for his height. In much retarded infants it may be necessary ultimately to use as many tablespoonfuls as the child should weigh for his age. The tolerance for carbohydrate and fats should never be overstepped. Fresh cow's milk, cream, butter and meat fat must be omitted for many months. If exacerbations occur should be omitted for years. Anorexia, abdominal distention, diarrheal or foamy stools necessitate the omission of carbohydrates, fats, fruits, vegetables and cod-liver oil. After an interval they may again be cautiously added. In exacerbations without apparent dietary or climatic causes, parenteral infections should be searched for, as tolerance decreases during such intercurrent diseases as pyeltits, pertussis and bronchitis.

Acidification of Milk with Vinegar.—DUNHAM (*Am. Jour. Dis. Child.*, 1925, **30**, 200) describes this method of acidulating cow's milk. This is added to counteract the effect of the buffer substance of the milk on the gastric acidity. The use of acetic acid in the form of household vinegar lessened the cost of acidulation, utilized a common and harmless article of the kitchen for this purpose and made the grocery store the source of supply. A pint of vinegar milk was made from 1 ounce of vinegar, containing 5 to 6 per cent acetic acid, to 15 ounces of cow's milk. The vinegar milk was given undiluted, except to infants younger than two months who received 4 ounces of water or gruel in the total daily feeding. Corn syrup diluted with an equal amount of water was added in the amount of 1 ounce of the diluted syrup to the pint of vinegar milk. The daily amount of the diluted syrup seldom exceeded 1½ ounces and this was reduced after cereal feedings were begun. This mixture was well tolerated as a routine food. Disturbance of the digestion was a rare occurrence, and was correctable by a temporary reduction of the sugar and fat elements of the food. The clinical results of feeding vinegar milk compare favorably with those of other types of acidulated milk. In this series some forty infants, chiefly of hospital and dispensary type were under observation on this mixture for periods of from one to six months. In no instance was it found necessary to change the type of feeding. The ages at beginning this diet ranged from four days to thirty-two months. The diagnoses included boarding babies, regulation of the diet, infantile atrophy, pylorospasm, syphilis, rickets and parenteral infections. The general appearance, contentment, nutrition, tissue turgor, musculature and rate of growth of the infants compare favorably, and in general parallel those on lactic and citric acid mixtures. The digestion was good. No abnormal amount of vomiting nor flatulency was observed. Substitution of vinegar for or by the other acids was sometimes made noticeable signs. Refusal of the mixture was not noted in any of the hospital cases. The stools

usually averaged from 2 to 3 daily and were of soft yellow consistency without free fat. In some instances where the amount of acid was less or the quantity of syrup was more than that recommended, frequency of the stools an intertrigo of the buttocks occurred. A return to the normal proportions usually effected a return to the normal digestion. Occasionally intercurrent parenteral infections were accompanied by indigestion with free fat in the stools. Replacement of the whole vinegar milk by skimmed vinegar milk and a reduction or temporary omission of the syrup was the dietary alteration of choice. In well babies changes in formulas were very infrequent. Usually one mixture would suffice for a period of from four to six weeks before another raise of from 2 to 4 ounces was necessary.

The Dick Test and Immunization Against Scarlet Fever.—Nesbit (*Jour. Am. Med. Assn.*, 1925, **84**, 805) has tested 2162 cases. Of these 927 were males and 1235 were females. Among the males 40 per cent were positive, 9 per cent were slightly positive, and 50 per cent were negative. With the females 40 per cent were positive, 12 per cent slightly positive and 48 per cent negative. Seven per cent reported having had scarlet fever, and of these 28 per cent were positive, 12 per cent were slightly positive and 60 per cent were negative. The severest reactions that were observed were 3 cases of urticaria. This developed soon after the administration of the toxin. In one school following the administration of toxin to 67, no pupils lost any time. In another school, 68 first doses were given, and 1 pupil stayed home half a day on account of a sore arm. Another pupil was reported to have had a rash with a mild illness after this dose. In the same child the second dose was followed by only a mild local reaction. The third dose was followed by a fever; two days later an euption occurred and a diagnosis of chickenpox was made which was probably the cause of the fever she had rather than the toxin. German measles was prevalent in some of the schools. This made it difficult to keep trace of every rash. In one school 57 children were given the Schick and Dick tests at the same time Every child was present the next day for the reading of the Dick test. Notices were not sent out to parents of the time that the tests would be given, as the children behave better when parents are not present. When the test was given, notice was sent home that the test had been given and that it was necessary for the child to be back at a specified time for the reading. Nesbit found the Dick test a satisfactory method of determining persons susceptible to scarlet fever. He feels that immunization without previous tests is not justified as a routine. The 3 doses of scarlet fever toxin given seemed to immunize about 65 per cent of the pupils. The group found to be still slightly positive on retests is probably slightly immune, but to determine this final tests with controls are required. In his experience so far no case of scarlet fever has developed in any person pronounced probably immune.

Therapeutic Results with Concentrated Scarlet Fever Antitoxin: A Preliminary Report.—Dick and Dick (*Jour. Am. Med. Assn.*, 1925, 84, 803) describe their technic in preparing and standardizing scarlet

fever antitoxin. In testing the antitoxin in a control group it was given in the cases that appeared most severe when they were first seen. The cases that were less severe during the first days of the disease were used as the controls. Mild cases were not included in the group. The cases classed as moderately severe were those patients in whom the ora temperature was at least 102°, and in whom there was a moderatel degree of toxemia. The cases classified as severe were characterized by high temperature with stupor, delirium or severe septic complications. In these two groups there were twice as many cases in the severe or antitoxin group as there were in the milder or control group To be of much value in the routine treatment of scarlet fever, a serum should have some influence on the frequency of complications. In the antitoxin group there were 2 cases of otitis media. No complications developed in those that received antitoxin on the first day of the rash. There were no cases of nephritis. The results were not so good in the cases without antitoxin. In the severe cases there was 1 death in the antitoxin series. This was due to a neglected mastoid infection. There was 1 case of marked cervical adenitis in a patient who received the antitoxin on the fifth day of the disease, when the glands were already enlarged. In studying these cases they were impressed by frequency of sinus infections in the more severe types of scarlet fever. Sinusitis was diagnosed clinically in 10 per cent of the moderately severe cases and in 58 per cent of the severe cases with marked toxemia or septic complications. In this series there was evidence that the sinus infection preceded the attack of scarlet fever or was coincident with it. It is possible that absorption of large amounts of toxin from the infected sinuses accounts for the severity of such cases. For the present two doses of antitoxin are given to patients with marked toxemia associated with sinusitis or in severe cases with septic complications. The best results were obtained when the total amount of antitoxin administered was given in one dose early in the disease. The antitoxin was given intramuscularly. Patients with a previous history of administration of horse serum were given preliminary small desensitizing doses before the therapeutic dose was injected. In early cases the rash is the most convenient indicator of the action of the antitoxin. If enough antitoxin has been given, the rash will fade definitely within twenty-four hours. There will be a marked improvement in the general condition of the patient, especially noticeable in the most toxic case. This improvement is accompanied by a fall in the temperature. One effect of the antitoxin is the unmasking of such complications as are already present. The removal of the toxic element of the disease makes the recognition of and the proper treatment of early complications more certain. The serum reactions in this series were comparable in every way with the reactions following diphtheria antitoxin. Any reaction to the serum is uncommon in persons who give no history of previous administration of horse serum.

OBSTETRICS

UNDER THE CHARGE OF

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End-results after Operation for Uterine Prolapse.—GRAD (*Am Jour. Obst. and Gynec.*, 1924, **8**, 163) has operated upon 53 cases of prolapse of the uterus using eight different operations; an average of $3\frac{5}{8}$ operations were required for each case of prolapse. Of the 53 cases, 66 per cent had the cervix amputated; 79 per cent had an anterior colporrhaphy; 94 per cent had perineorrhaphy; 43 per cent had interposition; 41 per cent had the uterosacral ligaments shortened and 13 percent had vaginal hysterectomy. From these experiences the writer concludes that childbirth is the cause of prolapse of the uterus. In 21 per cent of cases the condition develops after the first childbirth, and in 72 per cent the prolapse is of the third degree. Among these patients 39 per cent had prolapse after two or more children and of these 71 per cent had the third degree of prolapse. It could not be shown that instrumental delivery had anything to do with the production of uterine prolapse from the 41 per cent of instrumental deliveries, contrasted with the 59 per cent without instruments. As the age of the patient advances, the number of cases of extensive prolapse increases. Many of these cases were complicated by other conditions, and there is a mortality rate which accompanies operations upon these patients. Where the prolapse is pronounced in position, operation is useful. As to the results, the writer had 75 per cent of successes in his cases.

Yellow Spinal Fluid and Jaundice in the Newborn having Intracranial Hemorrhage.—SHARPE (*Am. Jour. Obst. and Gynec.*, 1924, **8**, 186) has studied this question for some time and finds, after repeated autopsies, that the intracranial anatomy of the bloodvessels in the newborn child differs from that of the adult, and that the newborn is much more susceptible to injury. When intracranial bleeding occurs, it is from one of three causes: From trauma, congestion, asphyxia or blood-disease of the newborn. Contrary to what is often alleged, syphilis, maternal toxemia, early low forceps applications and hemorrhagic disorders of the newborn are comparatively unimportant in causing cerebral hemorrhage. The signs vary, depending upon the amount and the location of the intracranial hemorrhage and edema. The mildest cases are usually overlooked and the routine lumbar puncture yielding bloody spinal fluid gives the first information concerning the condition. In one hundred consecutive deliveries 10 per cent had spinal fluid containing evidences of intracranial injury. In 4 this fluid was bloody, in 6 yellow, and in only 4 of these could red corpuscles be demonstrated. The condition of the anterior fontanelle is not a reliable index of a mild increase in the intracranial pressure. He distinguishes three

types of yellow spinal fluid: xanthochromia, erythrochromia and nonne syndrome. In this series, 6 cases contained yellow spinal fluid which probably results from the transudation of blood plasma when red corpuscles are absent; caused by minute hemorrhages when red blood corpuscles are present. In this series were 4 cases of icterus neonatorum, and only 1 had yellow spinal fluid in the writer's experience. Early lumbar puncture should be employed in the absence of shock, not only for diagnosis, but for its therapeutic value in cases of early cerebral hemorrhage and edema. Repeated spinal drainage every twelve to twenty-four hours is indicated, depending on the size of intracranial bleeding or the amount of cerebral edema as registered by the spinal mercurial manometer. The author employs a modified subtemporal decompression with cranial drainage only when drainage by lumbar puncture fails. In all suspected cases of hemorrhage in the newborn, manometric readings of intradural pressure should be taken with the spinal mercurial manometer.

A Contribution to the Genesis of Hydatid Mole.—KELLER (*Gynec. et Obst.*, 1924, **9**, 68) in 7 cases of hydatid mole found the characteristic degeneration in the villi, having its origin in anomalies in the circulation of the part. In the villi in moles it is remarkable that vessels are almost completely absent; what remains is the lacunæ, which are the original blood channels. The origin of these variations in circulation is not readily explained and is largely a matter of further histological study. In the same journal and from the Strassburg Clinic, RIEHL contributes a paper on "Marginal Placentæ." This contains illustrations with the report of microscopic study of the cases and statistics cited from other clinics. The writer's personal statistics are based upon 116 observations; 62 primiparæ, 53.44 per cent; 35 secundiparæ, 30.17 per cent; and 5 cases pregnant for the third time. The writer concludes that the important factor in these cases is the fibrous ring made up of fibrin of different development, some of it dense, some of it canalized and some marked by reticulation; in others the villi are more or less necrosed while still other specimens show the decidual cells in a necrotic condition more or less pronounced, with hemorrhage. In the first group of these marginal placentæ this fibrous ring is produced by the stagnation of blood in the antevillous space at the periphery of the placentæ. In the second group this fibrous ring develops at the end of the sixth or seventh month by unequal development of the two placental surfaces. There follows an extrachorial margin between the two placental surfaces. The third group of these placentæ, which is rare, is found where the placenta is inserted into the uterine cornu. This tubal insertion is accompanied by separation of the chorionic base of the superficial villi at the border of the placental lobe which covers the orifice of the tube. This is accompanied by hemorrhage and by the deposit of fibrin and by necrosis of the superficial villi. The result of these alterations is the formation of the fibrous ring, which is practically extrachorial. A small number of these placentæ are formed by the persistence of a portion of the decidua reflected at the margin of the placenta. From the clinical point of view, marginal placentæ occur most frequently with primiparæ and secundi-

paræ. This marginal placenta can be the cause of hemorrhage during pregnancy. These hemorrhages, accompanied by pain in the lower abdomen, can cause separation of the placentæ which, in the greater number of cases, is partial. In some very rare cases it is total and is followed by premature labor. There is a distinct causal relation between marginal placenta and premature separation of a placenta normally inserted. In other cases placental separation is the consequence and not the cause of hemorrhage. This is seen in marginal placenta inserted at the tubal orifice. These cases are frequently not recognized until the moment of delivery. In addition to rupture of the membranes in 116 of these cases, the author had seventeen in which atony of the uterus accompanied this condition. This complication was five times more frequent in these than in normal cases. The writer's studies do not indicate that this condition influences the development of the fetus.

Sudden Death following Labor.—An interesting contribution to sudden death with shock following labor in a toxic woman is made by SCHICKELE from his clinic in Strassburg (*Gynec. et Obst.*, 1924, **9**, 123). The patient was aged thirty-five, and in her second pregnancy; spontaneous labor was followed by hemorrhage and manual removal of the placenta, with good uterine contraction. Moderate anesthesia with ether had been employed and after delivery the patient complained of dyspnea, became gradually cyanosed, the pulse rapidly failed and an hour after delivery death occurred. Autopsy revealed an interesting condition. The substance of the liver was extensively disintegrated and necrotic. This degeneration was of different degrees at the periphery of the hepatic globules. The kidney lesions were unimportant and the manifestations of toxemia in the kidneys were in the first stage only. The patient did not give the slighest indication of eclamptic convulsions or threatened convulsions. The second case was that of a young woman whose labor lasted fifteen hours, terminated by a low forceps application followed by a temperature of 100.5° F. The extraction of the child was easily accomplished, the child was living and vigorous and the delivery was apparently without complications. An hour after the birth of the child the patient became suddenly pale, the pulse failed, there was no hemorrhage and four hours after delivery, sudden death. Autopsy revealed extensive lesions of the liver, no embolism, no lesions in the heart or other organs which would have produced such a result. Eight weeks before labor the patient had a fall which gave her a severe shock, but from which she recovered, and there was no evidence that this fall had anything to do with the fatal issue. At autopsy the liver showed extensive disintegration, dilatation of the capillaries, multiple hemorrhage and various stages of cellular degeneration. The kidney lesions in this case were very slight and there were some small hemorrhages in the cortical portion of the suprarenal capsules. This case showed at autopsy some of the lesions in the liver typical of eclampsia, but there were no symptoms of convulsions. The third case was a woman in her fourth pregnancy, with rachitic pelvis, Cesarean section, spinal anesthesia. The delivery of the child was complete in six minutes after the beginning of the operation under perfect anesthesia, when the pulse suddenly failed, the patient became

livid, respiration ceased and death ensued in a few moments. It was thought that the spinal anesthesia might have been the cause of the sudden death. Autopsy showed hyperemia of the abdominal organs, no lesions of the lungs, heart or kidneys, but in the liver the signs of yellow atrophy often seen in eclamptic cases. Microscopical examination showed at the periphery of the acini multiple foci of necrosis with fatty degeneration. The drug used in the spinal anesthesia was syncain.

GYNECOLOGY

UNDER THE CHARGE OF

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Irradiation Treatment of Urethral Caruncle.—A urethral caruncle, a small thing in itself, at times gives rise to no symptoms and may be discovered only in the course of a routine examination, but in many cases it cause burning, itching or even intense pain on urination. The old treatment of excision of these small tumors was often disappointing and frequently followed by recurrence. POMEROY and MILWARD (*Am. Jour. Roentgenol.*, 1924, **12**, 524) believe that they have attained their best results in the treatment of this condition by the use of radium. In their work nitrous oxide anesthesia is used because of the exquisite local tenderness and to permit a thorough pelvic examination. A small portion of the growth is excised for microscopic examination and the electrocautery is applied to the bleeding spot left at the site of the excision. They then apply screened radium to the urethral canal using 50 mg. of radium element screened with 0.5 mm. silver, 1 mm. brass and 1 mm. rubber, and the insertion of enough 5 mg. steel needles to occupy the growth and usually to surround the urethral canal. A sponge is placed over the meatus and the labia united over this by a removable suture passed through the outer end of the rubber covering the tube in the urethra. The radium is allowed to remain in position three to six hours, one treatment usually being sufficient. There is considerable local reaction after the treatment but this soon subsides and there have been no recurrences where this dosage has been used. They have not embedded unscreened emanation seeds in these cases but they believe that such seeds are suitable where the caruncle is sufficiently large to protect, by its size, the neighboring portions of the vulva from the buried emanation.

Milk Injections in Pelvic Infections.—For several years GELLHORN (*Am. Jour. Obst. and Gynec.*, 1924, **8**, 535) has been using parenteral protein therapy in the form of milk injections in the treatment of various

kinds of pelvic inflammations. He states that not all parts of the genital tract respond equally well to these injections. The tubes, the uterus and probably the bladder are favorably influenced while the ovaries seem to remain refractory. Exudates are brought to absorption or else a circumscribed suppuration is hastened so that they can be attacked surgically, but adhesions are not affected. Gonorrheal infection of the cervix, as a rule, remains likewise untouched by the treatment and the same may be said of gonorrheal foci in the urethra and rectum, which must be treated separately to prevent reinfection. The site of injection of the milk is preferably the gluteal musculature and if the needle is thin and sharp and the injection is made slowly, the procedure is not painful though the bulk of the fluid injected may cause a momentary discomfort. The initial dose is 5 cc, occasionally even less if the patient is very weak or the fever very high. The standard dose is 10 cc which, depending on individual circumstances, is reached with the second or third injection and then maintained through the course of treatment. The interval between injections is, as a rule, from three to five days according to the intensity of the reaction; in indolent patients it may occasionally be reduced to two days. In mild cases, 1 or 2 injections will often suffice; in others, more are required. The general reaction occurs from six to eight hours after treatment. The fever following the chill is usually of moderate degree though occasionally it may rise to 104°. The intensity of the initial reaction, which decreases after succeeding injections, is generally considered a favorable prognostic sign unless it be excessive, although satisfactory results have been obtained where there was hardly any general reaction. In any event, the general condition is affected but a very short time, twenty-four hours at most, after which the euphoria, which is mentioned by all writers is quite marked. The patients look and feel decidedly better and their appetites improve. Systematic white blood counts have revealed a hyperleukocytosis on an average of 20,000 to 25,000 on the day following the injection which receded to more normal figures within the next two days. An anaphylactic shock has never occurred in Gellhorn's cases and he does not anticipate any. While this alarming complication has been observed after intravenous injections of casein, only 3 such cases have been reported among the many thousands of intramuscular injections of milk. It may be that in these cases part of the injection had accidentally reached a vein, therefore Gellhorn makes it a point, before each injection, whether the needle has punctured a vessel. In spite of the ample scope of this form of treatment, its limitations must not be overlooked. There are several absolute contraindications, such as cardiac decompensation, diabetes and alcoholism. Whether pregnancy belongs to this group is still an open question.

Total versus Subtotal Hysterectomy.—The perennial question among gynecologists is the advisability of performing a subtotal or a total hysterectomy in the treatment of uterine fibroids, providing, of course, that the uterus must be sacrificed. Many arguments have been presented on both sides of the question and well-qualified surgeons have defended each operation, much to the exclusion of the other. In a report from Vienna, HALBAN (*Zentralbl. f. Gyn.*, 1924, **48**, 2674), a leading

Continental gynecologist, has analyzed the results in his clinic in a series of 342 cases. In this series there were 132 supravaginal amputations with a mortality of 4.5 per cent, 38 panhysterectomies with a mortality of 13.1 per cent, and 172 vaginal hysterectomies with a mortality of 5.2 per cent. Concerning the 13.1 per cent mortality in the series of total abdominal extirpations, presenting 5 patients, Halban states that these deaths were due to peritonitis in 2 cases, while in 2 others death was due to the severe anemia which had so affected the heart that the shock of operation could not be tolerated and he believes that these deaths should be charged against the heart rather than the operation. The fifth death was in a case in which a large intraligamentary myoma had been removed after which there was such a severe hemorrhage between the layers of the broad ligament that the internal iliac artery had to be ligated. Following this a thrombus broke loose and caused embolism of the femoral artery which was followed by gangrene of the leg. The leg was amputated but the patient died of sepsis. In the series of supravaginal amputations there were 6 deaths, 4 due to peritonitis and 2 due to myocardial degeneration. Of the 9 deaths in the series of vaginal hysterectomies, 2 were due to sepsis, 2 due to pneumonia, 1 due to severe anemia and 1 due to paralytic ileus: the other 3 deaths are not recorded. The above figures are taken from Halban's Clinic where the work was done by several operators and he begs to present the statistics of the cases which he personally operated upon over a long period of time (1911–1924). Including both myomata and myopathic hemorrhage cases, he has done 134 supravaginal amputations with 2 deaths (1.5 per cent mortality), 35 panhysterectomies with 2 deaths (5.7 per cent mortality), and 254 vaginal hysterectomies with no mortality. From these statistics it is readily seen that vaginal hysterectomy is the method of choice in Halban's hands.

OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF
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The Incidence and Pathogenesis of Tonsillar Concretions.—After an extensive historical review of his subject, WELLER (*Ann. Otol., Rhinol. and Laryngol.*, 1924, **33**, 79) reported the results of a careful research of the sections from a series of 1000 consecutive pairs of tonsils in order to have figures which represented minimum values. While no statistical record had been kept of calculi of large size, he believed that a conservative estimate would be 2 per cent. Much more common were the calculi discovered by microscopical examination alone, 80 cases showing calcareous deposits in the crypts of one or both tonsils—an incidence of 8 per cent. The average age of the cases in the series of 1000 was 18.7 years, while the average age of the 80 posi-

tive cases was 16.8 years. The author emphasized that the incidence as found in the 1000 cases may be taken as the minimum incidence figure for the 16,000 pairs of tonsils which have been examined in their laboratory. As clinical tonsillolithiasis usually occurs in late adult life, and the average age in the positive cases of this series was 16.8 years, it would seem to indicate a relatively slow rate of growth for larger calculi. Microscopical study of the genesis of tonsillar calcareous concretions showed that such deposits may occur in any portion of the tonsil. With rare exceptions it was only in the crypts that concretions reached such a size that they became clinical tonsilloliths. In the faucial tonsils the commonest modes of origin within the crypts were in the dead interior of colonies of mouth organisms and in masses of keratohyalin—59 per cent developing in the so-called "actinomyces-like" colonies of mixed mouth microörganisms and 41 per cent in the accumulated keratohyalin masses in the crypts. These are the chief sources of clinical tonsilloliths. Vegetable material, food débris, inflammatory exudate, desquamated epithelium and old blood from hemorrhage may also serve as the organic nucleus for calculus formation in the crypts. In the pharyngeal tonsils calculus formation occurred especially in mucopurulent exudate and in keratohyalin. In the lymphoid tissue of the tonsil calcification of old blood pus or caseous necrosis was found to occur, as in lymphoid tissue elsewhere. Tonsil calculi conformed to the general laws of calculus formation in that they developed only upon an organic nucleus in a state of necrosis or necrobiosis and that they could show, although but faintly, concentric lamination and radial striation. The very common association of cholesterin crystals with the beginnings of calculus formation in the tonsil indicated that the presence of lipoids and the formation of soaps may be an important part in the chemical mode of their development. As tonsillar calculi become larger, the author concludes "Their presence favors the origin and continuation of an active inflammatory process in the wall of the crypt in which they are situated."

The Significance of the Blood Picture in the Symptomatology and Therapy of Purulent Mastoiditis.—Having found that many of the well-known symptoms—such as pain on pressure, postauricular swelling, erythema and fever—of purulent mastoiditis are unreliable and uncertain, ROSENO (*Arch. Jour. Ohren-, Nasen-, u. Kehlropfhlk.*, 1924, **112**, 30) found that the blood picture furnished a delicate diagnostic criterion of this formidable condition. In 22 cases of suppurative mastoiditis, confirmed by operation, it was found that the leukocyte count ranged from 12,000 to 16,000, while the number of polymorphonuclear leukocytes varied from 80 to 88 per cent. When complications existed the white blood cells increased to 20,000 or 22,000 and the polymorphonuclears to 90 per cent. The authors believed that this hematological evidence yielded not only valuable early objective information on the presence of purulent mastoiditis but also was an index as to the necessity of operative interference.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

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Skin Infection of Rabbits with Hemolytic Streptococci Isolated from a Patient with Erysipelas.—A serum capable of warding off the injurious action of the streptococcus on the skin is described by RIVERS (*Jour. Exp. Med.*, 1925, **41**, 179). He isolated a streptococcus, whose virulence for rabbits intravenously or intraperitoneally was not marked. from a human case of erysipelas. The organism was morphologically and culturally typical of the Streptococcus hemolyticus and its virulence was maintained by occasional intracutaneous passages through rabbits. The bacteria from a twenty-four hour culture on blood agar were suspended in 8 cc Locke's solution and various dilutions of this were used in the inoculations, these being made into the shaved sides of the chests and abdomens of rabbits. Marked reactions were observed varying with the concentration of the inoculum. The reactions are fully described. Immune serum was prepared by 7 successive intracutaneous inoculations of 7 rabbits, during the course of which the skin reactions became progressively less marked. The sera were collected and pooled and at the same time the sera of 7 normal rabbits were collected. To 1 cc of immune serum and to 1 cc of the normal serum were added 1 cc of a streptococcus suspension and these mixtures were injected subcutaneously each on one side of the same rabbit. In many repetitions the protective power of the immune serum was continually characteristic, the normal serum having no protective effect. The intracutaneous method of demonstrating the immune properties of antistreptococcus serum may be of value, the author suggests, in determining the potency of sera for therapeutic uses, and for testing the specificity of different strains of streptococcus. The paper is well illustrated with photographs.

The Oxydase Reaction in Acute Myeloid Leukemia.—Staining methods for the determination of the nature of white cells in the blood have been developed almost without number. This in itself indicates that there are many features in respect to the granulation of white blood cells which are not well understood, and which can only be determined by the application of suitable dyes. PINEY (*Jour. Path. and Bact.*, 1925, **28**, 97) points out that there is a great divergence in the estimation of white cells depending upon the character of the stain used. It is found, for example, that specimens stained with Ehrlich's triacid stain demonstrate a greater number of neutrophile cells than when the Jenner's solution is used. It is found moreover that the oxydase reaction in the blood cells bears a direct relation to the presence of granules in the cytoplasm. Kardos had previously shown that the use of methyl green and orange G when introduced into Giemsa's solution, gave much

better results with neutrophile granules. The author has made some modifications of this stain and found it highly successful in demonstrating the myeloid leukocytes. When comparing the results of his staining in cases of acute leukemia with those of the Jenner solution it was found that the new staining method was more accurate in bringing to light slight granulation in myeloblasts which were entirely wanting in other staining methods. He found moreover that these results were in close harmony with those obtained by the oxydase reaction. The contention of the report is that the completely nongranular myeloblasts do not give a positive oxydase reaction and that the development of even a few granules in them is associated with the appearance of the reaction. It would appear that all gradations from the nongranular myeloblast may be traced to the heavily granuled myelocyte.

The Significance of Anaphylaxis in Penumococcus Immunity.—Working with a pneumococcus Type I isolated from the blood of a patient suffering from lobar pneumonia, McKenzie (*Jour. Exper. Med.*, 1925, **41**, 53) has attempted to determine the immunological significance of anaphylaxis. His general plan was to subject guinea-pigs to immunizing injections of pneumococcus, titering the immunity at frequent intervals and testing for the appearance and duration of allergy and anaphylaxis. His immunizing injections began with heat-killed eighteen-hour cultures and changed to fresh unkilled eighteen-hour cultures, bringing the animals during the course of four or five weeks to a state of immunity in which they survived 10,000,000 lethal doses of living culture. Every five to seven days 12 to 15 animals were taken from the batch of 150 to determine the degree of immunity attained and to demonstrate the presence of specific hypersensitiveness whenever it existed. The virulence of the pneumococcus was maintained at a fixed level by weekly animal passages. In testing for skin allergy and anaphylaxis the antigens used were: (1) Eighteen-hour broth cultures killed by heating to 60° C. for one hour; (2) filtrate from fresh eighteen-hour broth cultures; (3) an NaOH extract of a centrifuged, dried and powdered eighteen-hour culture, standardized by nitrogen content. Injections were made subcutaneously and intravenously, while the uterine strip method of Schultz-Dale was also used. Findings were unsatisfactory in the last named. The protective power of the serum was quantitatively determined at each observation. It was observed that decrease in the protective power of the serum occurs just prior to the period when anaphylaxis becomes demonstrable. The significance of this was not clear. Neither precipitins nor agglutinins were demonstrable at any time during the experiment. No cutaneous allergy to the derivatives of the pneumococcus used was demonstrable at any time. There was no change in trend of the immunity curve when anaphylaxis to the pneumococcus protein appeared. A high degree of immunity and a serum with strong protective power were obtained by the author in this experiment bearing, apparently, no relation to anaphylaxis. In a subsequent paper, *The Production and Significance of Cutaneous Allergy to Pneumococcus Protein*, McKenzie and Woo (*Jour. Exper. Med.*, 1925, **41**, 65) were unable to demonstrate any relation between cutaneous allergy—produced by intracutaneous injection of an alkaline

extract of pneumococcus products—and susceptibility to pneumococcus infection by intraperitoneal inoculation. Additional evidence in support of the idea that an allergy of the tuberculin type may be produced in the absence of an infection is brought out in the paper, although at the same time earlier studies have shown that allergy to derivatives of microörganisms is not an uncommon accompaniment of infection. The same strain of pneumococcus was employed as was used in the previous experiment. Skin allergy was easily and satisfactorily produced. Anaphylaxis was not demonstrable in these animals. Susceptibility to homologous infection in the allergic animals differed little or not at all from normal controls. The authors conclude that the relationship of allergy to immunity may vary with all types of infection and that no generalization is justifiable.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

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The Relation of Dose of Bacteria to Group Infection.—Bloomfield and Felty (*Jour. Exp. Med.*, 1924, **39**, 367), suggested in a previous paper on the basis of clinical observations and test-tube experiments, that the dose of bacteria and the degree of their vegetative activity were at least two factors which were significant in determining whether or not infection will develop in a susceptible host. Clinical observations on the effect of crowding suggest that in the presence of carriers of certain varieties of pathogenic bacteria a very high degree of intimate contact is necessary before spread of infection takes place at all; that as the degree of contact is reduced, there is not a gradual falling off in the number of secondary infections, but at a certain point they diminish with great abruptness to a figure approximating zero. In other words, it seems probable that people who are relatively resistant to a certain organism must receive a dose greater than some critical value before any infection will result, and that smaller doses, even if pathogenic bacteria are actually received, for example, into the upper air passages, will be quite inadequate, other things being equal, to colonize, to invade, or to produce disease. Such an idea explains the usual harmlessness of the diphtheria bacillus, streptococcus, or meningococcus carrier. His associates acquire the organisms, to be sure, but under ordinary conditions of contact only a subcritical dose in the sense indicated above. Recent studies by the same authors (*Jour. Exp.*

Med., 1924, **40**, 679) have been made of the peritoneal reaction in mice after injection of different bacteria in graded dose. Organisms were employed to which the animals were fairly resistant. Under these conditions it was found that as the dosage was decreased a more or less critical point was reached below which infection failed to be initiated. The possible clinical bearings of this observation are discussed.

Observations on the Diphtheria Carrier as an Agent in the Spread of Diphtheria.—MEADER (*Jour. Am. Med. Assn.*, 1924, **83**, 1132) states that it would appear that diphtheria patients are more likely to be agents in the spread of diphtheria than are carriers, but it cannot be denied that carriers who harbor organisms capable of producing the disease may be very potent agents in the spread of infection. He believes, however, that carriers of diphtheroids who have not been associated with clinical cases of diphtheria may be disregarded from a public-health point of view.

A Comparison of Physical Defects in University Students from Rural and Urban Districts.—SHEPARD and DIEHL (*Jour. Am. Med. Assn.*, 1924, **83**, 1117) examined students entering the University of Minnesota for the purpose of detecting departures from normal. The results were as follows: Students raised in villages of from 50 to 1000 population have more physical defects than students raised in other communities. Multiple defects are also common in this group. Students raised on farms show more physical defects than those raised in towns or large cities, about the same number as those from small cities and less than those raised in villages. Students raised in towns of from 1,000 to 5,000 population show less physical defects than any others except those from large cities. Students raised in small cities of from 5,000 to 50,000 population are exceeded in total physical defects only by students from villages. Students raised in cities of more than 50,000 population show the lowest number of physical defects.

Tularemia Infection in Ticks of the Species Dermacentor Andersoni Stiles in the Bitter Root Valley, Mont.—PARKER, SPENCER and FRANCIS (*Pub. Health Rep.*, 1924, **39**, 1057) suggest that tularemia may be communicated to man through ticks. The infection has been found in immature and in adult ticks. The infection survives in the insects for a period of several months. It was found that a number of small mammals in the tick region are susceptible to tularemia and doubtless help to perpetuate it.

The Thermic and Leukocytic Response of the Rabbit to Inoculation with the Virus of Measles and their Value as Criteria of Infection.—Among the laboratory animals, monkeys, guinea pigs and rabbits have been found to be susceptible to the virus of measles. That rabbits may be successfully infected has been demonstrated by the combined, investigations of Harde (1921), Nevin and Bittmann (1921 and 1923) Grund (1922) and Duval and d'Aunoy (1922). SCOTT and SIMON (*Am. Jour. Hyg.*, 1924, **4**, 559) conclude from their experiments that a sustained rise in temperature with its acme occurring at a certain time, coupled with an amphophilic leucopenia, constitute the most character-

istic symptoms of a measles infection in the rabbit, and that with proper controls the thermic and leucocytic responses may well serve as criteria of infection with this virus.

A Note on the Relationship of Tonsillectomy to the Occurrence of Scarlet Fever and Diphtheria.—DOULL (*Pub. Health Rep.*, 1924, **39**, 1833) made surveys of the white school population of wards, 5, 6, 7, 8, 9 and 10 of the city of Baltimore, and found that the percentage of children having had the tonsils removed varies from approximately 7 per cent at ages five and six years to 19 per cent at ages thirteen and fourteen years. A study of a consecutive series of 224 cases of diphtheria of school age and living in the same area of the city showed that only 2 (0.9 per cent) of the children had had tonsillectomy performed. This is a very much smaller number than would be expected in a sample of this size and age distribution selected at random from the school population. In a sample of 193 cases of scarlet fever in children of school age, 19 (9.8 per cent) were found to have had the tonsils removed prior to attack. This number does not differ significantly from that expected in a random sample of the school population similarly constituted as to age. The author states that he believes the results of his studies justify the conclusion that children whose tonsils have been removed are distinctly less liable to diphtheria than those who have not had this operation performed; whereas in scarlet fever no significant difference is shown. General conclusions as to the relationship which tonsillectomy bears to either of these infections, diphtheria or scarlet fever, require more observations in other localities.

How Salt Preserves.—ROCKWELL and EBERTZ (*Jour. Infect. Dis.*, 1924, **35**, 573) state that the preserving of proteins with salt involves more than its dehydration effect, there being at least four factors, namely: Dehydration, direct effect of chlorine ion, removal of oxygen, sensitization against carbon dioxid and interference with rapid action of proteolytic enzymes.

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